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Call for Applications

Editor, *Clinical Thyroidology*

The Publications Committee of the American Thyroid Association (ATA) is soliciting applications for the position of Editor of *Clinical Thyroidology*. The new editor will officially assume responsibility for the journal on January 1, 2008, but should be willing to assume some responsibilities this fall. The Committee seeks an individual who will continue the growth, quality, reputation, and scholarship of this important ATA publication. The applicant should be a respected thyroid clinician or investigator who is well organized, innovative, energetic, and dedicated to making *Clinical Thyroidology* increasingly indispensable to clinicians and scientists alike. She/he should have experience as a writer and as an editor, associate editor, or editorial board member of a peer-reviewed journal. The initial appointment will be for a three-year term renewable by mutual agreement between the editor and the ATA.

Applicants should submit a cover letter, their curriculum vita, and a general statement outlining their vision and goals for *Clinical Thyroidology* to Matthew Ringel, M.D., Chair of the ATA Publications Committee, by email to Ms. Bobbi Smith, CAE, ATA Executive Director (*bsmith@thyroid.org*).

The deadline for applications is September 14, 2007. The applications will be reviewed during September, and candidates should be available to be interviewed in person at the 78th Annual Meeting of the American Thyroid Association in New York City, October 3–7, 2007. Questions regarding this position may be directed to Matthew Ringel, M.D., Search Committee Chair (*matthew.ringel@osumc.edu*, or 614-292-4356) or to the present editor, Robert D. Utiger, M.D. (*rutiger@partners.org*, or 617-525-5171).

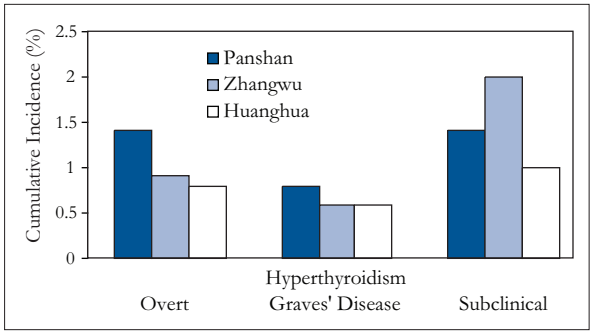
Chronically high iodine intake is not associated with an increased incidence of hyperthyroidism

Yang F, Shan Z, Teng X, Li Y, Guan H, Chong W, Teng D, Yu X, Fan C, Dai H, Yu Y, Yang R, Li J, Chen Y, Zhao D, Mao J, Teng W. Chronic iodine excess does not increase the incidence of hyperthyroidism: a prospective community-based epidemiological survey in China. Eur J Endocrinol 2007;156:403-8.

SUMMARY

Background Variations in iodine intake have been associated with variations in the frequency of hyperthyroidism in some studies. In this study, the cumulative incidence of overt hyperthyroidism, overt hyperthyroidism caused by Graves' disease, and subclinical hyperthyroidism were determined in different communities in China in which iodine intake varied substantially but had not changed in over five years.

Methods In 1999, 3671 subjects living in three communities in China completed questionnaires about thyroid disease; had measurements of serum thyrotropin (TSH), free thyroxine (T_4), anti-TSH-receptor antibodies, antithyroid peroxidase (anti-TPO) antibodies, and urinary iodine; and underwent thyroid ultrasonography. The same procedures were done in 3108 of the subjects (80 percent) in 2004.



Overt hyperthyroidism was defined as low serum TSH and high serum free T_4 concentrations. Overt hyperthyroidism caused by Graves' disease was additionally defined as diffuse thyroid enlargement and a high serum anti-TSH receptor antibody or a high serum anti-TPO antibody concentration. Subclinical hyperthyroidism was defined as low serum TSH and normal serum free T_4 concentrations.

The three communities were Panshan (median urinary iodine excretion, 97 μg/L), Zhangwu (362 μg/L), and Huanghua (597 μg/L). The urinary iodine values in these communities were very similar in 1999 (103, 374, and 615 μg/L, respectively). The people in Panshan made their salt from iodine-poor water. Zhangwu had been a region of iodine deficiency, but iodized salt was made available in 1996. In Huanghua, the water had long contained a high concentration of iodine. These communities were considered to have iodine deficiency, more than adequate iodine intake, and excessive iodine intake, respectively.

Results The mean age of the 3018 subjects was 43 years; there were 2316 women and 702 men. The 5-year cumulative incidence of overt hyperthyroidism, overt Graves' hyperthyroidism, and subclinical hyperthyroidism was similar in all three communities (Figure).

Ninety-two of the 115 subjects (80 percent) who had subclinical hyperthyroidism in 1999 were studied again in 2004. None received antithyroid therapy in the interim. In 2004, 66 (72 percent) were euthyroid, 18 (20 percent) still had subclinical hyperthyroidism, 5 (5 percent) had overt hyperthyroidism, and 3 (3 percent) had subclinical hypothyroidism. There were no differences in the changes in the three communities.

Conclusion The cumulative 5-year incidence of overt hyperthyroidism, overt hyperthyroidism caused by Graves' disease, and subclinical hyperthyroidism is similar in subjects in different communities in which iodine intake varied from mild deficiency to excess.

COMMENTARY

Iodine-induced hyperthyroidism typically occurs in two groups of people. One group consists of people living in regions of iodine deficiency (urinary iodine excretion <100 μg/L), in whom hyperthyroidism occurs in the first year or two after iodine intake is increased. They have TSH-independent T_4 and triiodothyronine (T_3) production caused by a nontoxic nodular goiter or Graves' disease, but do not have hyperthyroidism unless iodine intake is sufficient (>150 μg daily) to allow production of excess T_4 and T_3. The frequency of this type of iodine-induced hyperthyroidism is low, and it mostly affects older people. It probably depends on the extent of thyroid autonomy and the dose of iodine, and its frequency rises and falls because hyperthyroidism develops in those at risk soon after the increase in iodine intake.

The second group consists of people living in regions of iodine sufficiency who have a nontoxic nodular goiter, in which one or more of the nodules transport iodine poorly or not at all. Hyperthyroidism develops when iodine intake greatly increases, for example, by injections of iodinated radiographic contrast agents, amiodarone therapy, or milligram doses of inorganic iodine. The presumed mechanism of this type of iodine-induced hyperthyroidism is that extracellular-fluid iodine concentrations are suddenly sufficiently high to allow enough iodine to enter autonomous nodules lacking iodine transporters by diffusion to allow excessive T_4 and T_3 production. This type of iodine-induced hyperthyroidism does not occur in people with Graves' disease, because iodine transport into all thyroid cells is increased, and substantial increases in intrathyroidal iodine have antithyroid actions.

What is the relationship between chronic iodine intake and hyperthyroidism? According to Yang et al., there is none, at least in people with a rather broad range—but not the extremes—of iodine intake.

Robert D. Utiger, M.D.

Congestive heart failure is rare in patients with hyperthyroidism, and when present is associated with atrial fibrillation

Siu CW, Yeung CY, Lau CP, Kung AW, Tse HF. Incidence, clinical characteristics and outcome of congestive heart failure as the initial presentation in patients with primary hyperthyroidism. Heart 2007;93:483-7.

SUMMARY

Background Patients with hyperthyroidism may have symptoms and signs of cardiovascular dysfunction, including congestive heart failure. However, its frequency is low, and little is known about its risk factors or its outcome. In this study, the prevalence, characteristics, and outcome of congestive heart failure in a large group of patients with hyperthyroidism were determined.

Methods The study subjects were 591 consecutive patients (451 women, 140 men; mean age, 45 years) with hyperthyroidism caused by Graves' disease (61 percent) or toxic multinodular goiter (39 percent). Patients with a history of any cardiovascular disease were excluded.

The diagnosis of congestive heart failure was based on the presence of two of seven major criteria: nocturnal dyspnea, orthopnea, high jugular venous pressure, rales, a third heart sound, cardiac enlargement, and pulmonary edema; or one major criterion and two of seven minor criteria: edema, night cough, exertional dyspnea, hepatomegaly, pleural effusion, tachycardia, and recent weight loss. After diuretic, β-adrenergic antagonist, and antithyroid drug therapy for a few days, the patients underwent transthoracic echocardiography. Left ventricular systolic dysfunction was defined as a left ventricular ejection fraction (LVEF) ≤50 percent. The studies were repeated three months later.

Results Thirty-four patients (6 percent) had congestive heart failure. They differed in several respects from the other 557 patients, especially in the frequency of atrial fibrillation (Table 1), but not in the frequency of Graves' disease or toxic multinodular goiter or in serum free thyroxine values.

Sixteen of the 34 heart-failure patients (47 percent) had left ventricular (LV) systolic dysfunction when first studied (Table 2).

Table 1. Characteristics of 591 Patients with Hyperthyroidism with or without Congestive Heart Failure.*

	Heart Failure (n=34)	No Heart Failure (n=557)
Women/men	14/20	437/120
Mean age (yr)	66	44
Hypertension	11 (32%)	39 (7%)
Diabetes mellitus	5 (15%)	27 (5%)
Mean duration of symptoms (d)	39	32
Mean heart rate (bpm)	138	100
Atrial fibrillation	32 (94%)	50 (9%)

*P≤0.01 for all between-group comparisons.

Table 2. Characteristics of 34 Patients with Hyperthyroidism and Congestive Heart Failure according to the Presence or Absence of Systolic Dysfunction after Initial Therapy.

	Systolic Dysfunction (n=16)	No Systolic Dysfunction (n=18)
Women/men	2/14	12/6*
Mean age (yr)	58	72*
Atrial fibrillation	14 (88%)	18 (100%)
Mean LV end-diastolic length (cm)	5.3	4.3*
Mean LVEF (%)	29	62*

*P≤0.03, as compared with the systolic-dysfunction group.

One patient in the systolic-dysfunction group died of congestive heart failure soon after diagnosis. In the remaining 15 patients, the heart rate was controlled (<90 bpm) in 5 days (mean), 6 of 13 (47 percent) with atrial fibrillation had a sinus rhythm 328 days later, and 5 had persistent systolic dysfunction. Among the no-systolic-dysfunction group, the heart rate was controlled in 5 days, and 8 of 18 (44 percent) with atrial fibrillation had a sinus rhythm 121 days later.

Conclusion Few patients with hyperthyroidism have congestive heart failure. Among those who do, nearly all have atrial fibrillation, and approximately half have left-ventricular systolic dysfunction, which may persist after effective antithyroid therapy.

COMMENTARY

The high cardiac output state in patients with hyperthyroidism is caused by a rapid heart rate and increased stroke volume, and their decreased exercise tolerance reflects decreased cardiovascular reserve. Hence, any adverse event that might impair the overall efficiency of the cardiovascular system, such as abnormalities in preload or after load, loss of sinus rhythm, or decreased myocardial contractility, may precipitate congestive heart failure.

In most patients with a reduced left ventricular ejection fraction and congestive heart failure in this study, combined diuretic, β-adrenergic, and antithyroid drug therapy resulted in rapid and complete or near-complete recovery of cardiac function. The tachycardia and atrial fibrillation associated with hyperthyroidism are causes of cardiomyopathy, left ventricular dysfunction, and chronic heart failure in these patients, and the changes are reversible when abnormalities in cardiac rate or rhythm are controlled.

Several cases of cardiomyopathy have been reported in patients as long as 15 years after successful treatment of hyperthyroidism. The cause of this cardiomyopathy is not known, nor is it known whether myocardial necrosis contributes to it. No specific histopathologic abnormalities were found in myocardial biopsies from these patients, although some who had a low left ventricular ejection fraction and congestive heart failure had scintigraphic evidence of myocardial damage.

Prompt recognition is essential to identify and treat patients with hyperthyroidism who have cardiomyopathy to minimize the risk of long-term cardiac dysfunction, and hyperthyroidism should be considered as a possible cause of cardiomyopathy in patients in whom no other cause is evident.

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A low dose of methimazole is nearly as effective as a higher dose of methimazole or propylthiouracil in patients with Graves' hyperthyroidism

Nakamura H, Noh JY, Itoh K, Fukata S, Miyauchi A, Hamada N. Comparison of methimazole and propylthiouracil in patients with hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab 2007;92:2157-62.

SUMMARY

Background Many patients with hyperthyroidism are treated with methimazole or propylthiouracil. These drugs have long been available, but the optimal initial doses and their relative efficacy and safety continue to be debated. In this study, the efficacy and safety of methimazole and propylthiouracil were compared in patients with Graves' hyperthyroidism.

Methods The study subjects were 303 patients with Graves' hyperthyroidism (mean age, 40 years), as defined by clinical findings; low serum thyrotropin (TSH) and high serum free thyroxine (T_4), free triiodothyronine (T_3), and TSH-receptor antibody concentrations; and high thyroid radioiodine uptake values.

The patients were randomly assigned to treatment with 15 mg of methimazole once daily, 15 mg of methimazole twice daily, or 100 mg of propylthiouracil three times daily for 12 weeks. They were evaluated at base line and after treatment for 4, 8, and 12 weeks. Adverse effects were systematically evaluated and serum alanine aminotransferase, aspartate aminotransferase, free T_4, and free T_3 were measured at these times.

Results Two hundred sixty-three patients completed the 12-week study. The most effective treatment at all times was 30 mg daily of methimazole, but the differences in favor of this dose were small (Table 1).

Serum free T_3 concentrations were normal in 35 to 49 percent of the patients in the three groups at 4 weeks, and normal at 8 weeks in more patients in the methimazole 30-mg/day group than in the propylthiouracil 300-mg/day group (76 vs. 57 percent; $P<0.05$) and 12 weeks (90 vs. 63 percent; $P<0.001$).

Table 1. Frequency of Normal Serum Free T_4 Concentrations in Patients with Graves' Hyperthyroidism Treated with Methimazole or Propylthiouracil.*

Dose	4 Weeks	8 Weeks	12 Weeks
Methimazole, 15 mg/day	40/109 (37%)	84/120 (70%)	94/109 (86%)
Methimazole, 30 mg/day	48/91 (53%)**	74/91 (81%)	82/85 (96%)**
Propylthiouracil, 300 mg/day	28/73 (38%)	50/73 (68%)	54/69 (78%)†

*Patients with normal serum free T_4 concentrations/all patients in that dose group.
**$P<0.05$, as compared with 15 mg/day of methimazole.
†$P=0.001$, as compared with 30 mg/day of methimazole.

Among the 197 patients with base-line serum free T_4 concentrations <7.0 ng/dl (90 pmol/L), the results were only slightly superior in the methimazole 30-mg/day group. In the 66 patients with base-line serum free T_4 concentrations ≥7.0 ng/dl (90 pmol/L), the concentrations were normal in the methimazole 30-mg/day group considerably more often, by about 30 percent, at all times.

The overall frequency of adverse effects and that of most specific adverse effects were higher in the propylthiouracil 300-mg/day group (Table 2).

Table 2. Adverse Effects of Methimazole and Propylthiouracil.

	Methimazole, 15 mg/day (n=137)	Methimazole, 30 mg/day (n=130)	Propylthiouracil, 300 mg/day (n=104)
Total adverse effects	14%	30%	52%
Drug changed or stopped	7%	22%	38%
Hepatotoxicity*	7%	7%	27%
Urticaria or other skin rash	7%	22%	22%

*Serum aminotransferase concentration >2 times the upper limit of normal, leading to cessation of treatment.

Conclusion Among patients with Graves' hyperthyroidism, treatment with 15 mg/day of methimazole is nearly as effective and is safer than 30 mg/day of methimazole and as effective and safer than 300 mg/day of propylthiouracil.

COMMENTARY

Methimazole is about 20 times more potent than propylthiouracil in reducing serum T_4 and T_3 concentrations in patients with hyperthyroidism. Higher doses of methimazole are more rapidly effective than lower doses, and it is equally effective when given once daily or in divided doses. In contrast, propylthiouracil is more effective when given in divided doses (1). Methimazole is safer than propylthiouracil, and lower doses of methimazole are safer than higher doses, although the frequency of agranulocytosis is the same with both drugs. High doses of propylthiouracil lower serum T_3 concentrations more in the first days of therapy, but this effect is short-lived and probably not clinically important.

An important unanswered question is whether treatment with methimazole or propylthiouracil is more likely to result in remission of Graves' disease. Both drugs may have an immunosuppressive action, but it may be due to their antithyroid action. The frequency of sustained remission was similar (approximately 40 percent) in 313 patients treated with 10 or 40 mg of methimazole daily for one year (2), but in another one-year treatment study, 15 of 25 patients (71 percent) treated with propylthiouracil had a sustained remission, as compared with 10 of 25 patients (40 percent) of those treated with methimazole (3).

Methimazole is the best antithyroid drug for most patients with Graves' hyperthyroidism, and the initial dose should rarely exceed 15 mg, taken once daily, based on considerations of efficacy and safety.

Robert D. Utiger, M.D.

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The addition of Chinese herbal medicines to antithyroid drug or radioiodine therapy has little benefit in patients with hyperthyroidism

Zen XX, Yuan Y, Liu Y, Wu TX, Han S. Chinese herbal medicines for hyperthyroidism. Cochrane Database Syst Rev 2007, (2): CD005450.

SUMMARY

Background In China and other countries, patients with hyperthyroidism are often treated with herbal medicines combined with an antithyroid drug or radioiodine (I-131). These medicines have been thought to ameliorate the symptoms of hyperthyroidism and to have antithyroid or immunosuppressive actions. This systematic review was undertaken to determine the efficacy of Chinese herbal medicines in combination with an antithyroid drug or I-131 as treatment for patients with hyperthyroidism.

Methods MEDLINE, EMBASE, the Cochrane Library, the Chinese Biomedical Database, and other databases were searched for randomized trials in which the combination of Chinese herbal medicines and an antithyroid drug or I-131 were compared with an antithyroid drug or I-131 in patients with hyperthyroidism. The cause was Graves' disease in four trials, but it was not specified in the others.

The primary outcomes were the relapse rate one year after cessation of treatment (three trials) and hypothyroidism after I-131 therapy (one trial). The secondary outcomes included amelioration of symptoms of hyperthyroidism and changes in thyroid function. The methodologic quality of the trials was assessed according to the method of allocation to treatment, patient or physician awareness of treatment-group assignment, and adequacy of follow-up. The authors of trials meeting these criteria were interviewed to confirm the study procedures. Only differences that were statistically significant ($P<0.05$) are described below.

Results The search identified 635 trials, of which 103 were initially thought to be eligible for inclusion in the review. After further review and interviews with authors, 13 were considered to be randomized trials suitable for analysis. These trials included 1770 patients (mean, 136), of whom 1333 were women and 437 were men (mean age, 32 years; range, 12 to 68). The duration of hyperthyroidism ranged from 1 month to >10 years.

The herbal medicines were given as capsules, liquid, or teas, or by intravenous injection. The daily dose consisted of from 5 to 30 g each of 2 to 13 ingredients (mean, 9). Overall, 55 herbs were used, and the highest total daily dose was 185 g. The trial investigators prepared most of the herbal-medicine formulations. They were given concomitantly with methimazole or propylthiouracil (and in some trials with each drug separately) for 2 weeks to 2 years in 11 trials or after I-131 with an antithyroid drug for 2 weeks to 3 months in two trials. The duration of treatment ranged from 10 days to 2 years and the duration of follow-up from 1 month to 4 years.

As compared with an antithyroid drug alone, the relapse rates were lower in three trials in which the patients were treated with both herbal medicines and an antithyroid drug, and in one trial hypothyroidism was less frequent in patients treated with both after I-131 therapy. During treatment, symptoms of hyperthyroidism improved in more patients receiving combined therapy in six trials.

One or more of the following—serum TSH and thyroid hormone concentrations—changed toward or to normal more often in 12 trials of combined therapy, and there were no differences in one or more of these analytes in 12 trials.

The quality of the trials was considered poor, in terms of methods of randomization, assessment of compliance, reporting of withdrawals, and completeness of presentation of results

Conclusion Chinese herbal medicines, when given in conjunction with methimazole or propylthiouracil alone or after I-131, have little benefit as adjunctive therapy in patients with hyperthyroidism.

COMMENTARY

This study represents a painstaking effort to categorize many studies of the use of Chinese herbal medicines for the treatment of hyperthyroidism, most likely that caused by Graves' disease or a toxic nodular goiter. The main reason trials were excluded was that treatment-group assignment was not random, but even when it was that information often was not provided in the published paper and became known only after these authors questioned the investigators (not a reassuring finding). Wisely, the authors did not attempt a meta-analysis, given the heterogeneity of the trials.

Some of the results suggest that herbal medicines might have propranolol-like effects or antithyroid effects, but since they were always given as formulations of varying composition and the formulations differed in every study, any benefits cannot be ascribed to any one formulation, much less to any one individual constituent. Certain foods contain antithyroid substances, including iodine (kelp), flavonoids (millet seed), thiocyanate (cassava), perchlorate (many foods, depending on the content in ground water), and other goitrogens. Whether any of the 55 herbal medicines included in the complex formulations used in these 13 studies contain any of these substances, or other antithyroid substances, is not known, but seems possible. If so, they alone might cause hypothyroidism, particularly in patients with an underlying thyroid disorder such as chronic autoimmune thyroiditis.

Formulations of herbal medicines are used in traditional Chinese herbal medicine to treat many disorders. Physicians in the United States may occasionally see patients with hyperthyroidism so treated. They are more likely to see patients with hypothyroidism, but neglect to ask if they are taking Chinese herbal medicines..

Robert D. Utiger, M.D.

Antithyroid drug therapy given before or after radioactive iodine decreases the efficacy of radioiodine in patients with hyperthyroidism

Walter MA, Briel M, Christ-Crain M, Bonnema SJ, Connell J, Cooper DS, Bucher HC, Müller-Brand J, Müller B. Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials. BMJ 2007;334:514-20.

SUMMARY

Background Many patients with hyperthyroidism are treated with radioiodine (I-131). Some also are treated with an antithyroid drug before, at the time of, or after the administration of I-131. This systematic analysis was done to determine the effect of adjunctive antithyroid drug therapy on the efficacy of I-131 therapy.

Methods Studies of combined antithyroid drug and I-131 therapy in patients with hyperthyroidism were identified by a systematic review of the literature. For inclusion in the analysis, the study subjects had to be adults who were randomly assigned to receive an antithyroid drug and I-131 or I-131 alone and who were followed for at least six months after I-131 was given. The quality of the trials was evaluated for concealment of study-group assignment, completeness of follow-up, and other features. The outcomes evaluated were persistent or recurrent hyperthyroidism and hypothyroidism.

Results Fourteen trials met the criteria for inclusion in the study. They included 1306 patients, of whom 660 (51 percent) were treated with an antithyroid drug and I-131 and 646 (49 percent) with I-131 alone. The numbers of patients in the trials ranged from 24 to 189. Their mean age ranged from 37 to 60 years, 78 percent were women, and 82 percent had hyperthyroidism caused by Graves' disease. Trial quality was considered poor.

The antithyroid drug was given before I-131 in five trials, at the time of or after I-131 in seven, and before and after I-131 in two. Methimazole was given in six trials, carbimazole in three, propylthiouracil in four, and methimazole and propylthiouracil in one. In the patients pretreated with an antithyroid drug, the drug was discontinued 2 to 7 days before I-131 therapy, at which time the patients were euthyroid. The antithyroid drug was started at the time of I-131 therapy or up to 7 days later in the other studies. All the patients had a high thyroid radioiodine uptake immediately before I-131 therapy, and the mean dose of I-131 was 8.9 mCi (329 MBq).

Persistent or recurrent hyperthyroidism was more common in the antithyroid-drug and I-131-therapy group than in the I-131 group (Table). Conversely, hypothyroidism was less common in the antithyroid-drug and I-131-therapy group.

Table. Risk of Persistent or Recurrent Hyperthyroidism and Hypothyroidism after I-131 Therapy in Patients with Hyperthyroidism Treated with an Antithyroid Drug and I-131 or I-131 Alone.

	Drug/No Drug	Summary Risk (95% CI)
	Persistent or Recurrent Hyperthyroidism	
Before I-131	28%/19%	1.5 (1.1-2.0)*
At or after I-131	23%/19%	1.3 (1.0-1.7)**
	Hypothyroidism	
Before I-131	25%/32%	0.8 (0.6-1.0)†
At or after I-131	14%/24%	0.6 (0.4-0.8)*

CI denotes confidence interval. *P=0.01, **P=0.03, †P=0.06.

The results for both outcomes in the patients treated with methimazole, carbimazole, or propylthiouracil were similar. The frequency of successful treatment and of hypothyroidism increased with increasing doses of I-131 in both treatment groups.

Conclusion Among patients with hyperthyroidism, antithyroid drug therapy before or at the time of and after I-131 therapy results in a higher frequency of persistent or recurrent hyperthyroidism and a lower frequency of hypothyroidism, as compared with I-131 alone.

COMMENTARY

The issue of treating patients who have hyperthyroidism with an antithyroid drug before or after I-131 therapy is clinically important. I-131 is often given without any antithyroid drug in patients with mild to moderate hyperthyroidism, and appropriately so. In these patients, whatever their serum thyroid hormone concentrations, there is little risk of a clinically important exacerbation of hyperthyroidism after I-131 therapy, and there is no reason to put them at risk for an adverse effect of an antithyroid drug.

When hyperthyroidism is severe, the patients are elderly, or they have cardiovascular manifestations of hyperthyroidism, it is common practice to give an antithyroid drug to control symptoms quickly and to reduce the risk of exacerbation of hyperthyroidism after I-131 therapy. The drug is usually stopped a few days before thyroid uptake of I-131 (or I-123) is measured and I-131 therapy is given, and it may be resumed later. Some patients are given an antithyroid drug only after I-131 is given to reduce symptoms during the interval between I-131 administration and the response to it.

It is important, therefore, to know whether antithyroid drug therapy at any time reduces the efficacy of I-131 therapy and the frequency of hypothyroidism. The review by Walter et al. summarizes the results of multiple studies of this issue. They found that administration of an antithyroid drug either before or after I-131 therapy resulted in small but in some instances statistically significant increases in the risk of persistent or recurrent hyperthyroidism and decreases in the risk of hypothyroidism.

While an antithyroid drug should not be given routinely before or after I-131 therapy, some patients probably do benefit from the drug when given before I-131 therapy, if only because it more quickly decreases thyroid secretion. Whether there is any benefit from antithyroid drug therapy started at the time of or after I-131 therapy is less clear.

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Serum C-reactive protein concentrations increase soon after radioiodine therapy in patients with hyperthyroidism

Sari O, Tunc R, Kisakol G, Dostbil Z, Serdengecti M. Acute-phase response after radioiodine treatment in hyperthyroidism. Endocrinologist 2007;17:89-91.

SUMMARY

Background Radioiodine (I-131) therapy for hyperthyroidism results in acute thyroid inflammation, which occasionally causes clinically evident thyroiditis, and later autoimmunization, with increases in serum antithyroid antibody concentrations. In this study, serum thyroid hormones, thyrotropin (TSH), thyroglobulin, antithyroid antibodies, and nonspecific markers of inflammation were measured before and for several months after I-131 therapy in patients with hyperthyroidism.

Methods The study subjects were 26 patients with hyperthyroidism (18 women, 8 men; mean age, 48 years). Nineteen patients had hyperthyroidism caused by Graves' disease and seven a toxic nodular goiter. They were treated with 8 to 15 mCi (296 to 555 MBq) of I-131.

Leukocyte and platelet counts, hemoglobin and hematocrit, erythrocyte sedimentation rate (ESR), and C-reactive protein were measured before and 1 and 3 days, 1 and 4 weeks, and 3 months after I-131 therapy. Serum free thyroxine (T_4), TSH, thyroglobulin, and antithyroid microsomal antibodies were measured before and 4 weeks and 3 months after therapy.

Results Serum free T_4 concentrations decreased and TSH concentrations increased after I-131 therapy in all patients (results not given). The mean serum thyroglobulin concentration increased 4 weeks after therapy and then decreased (Table).

Table. Changes in Hematologic Values, ESR, C-Reactive Protein, and Antithyroid Microsomal and Antithyroglobulin Antibody Concentrations after I-131 Therapy in Patients with Hyperthyroidism.

	Base Line	1 Day	3 Days	1 Week	4 Weeks	3 Months
Leukocyte count ($\times 10^9$/L)	7.2	7.0	7.0	6.4	6.2	6.8
ESR (mm/hr)	8	7	9	11	11	14
Serum						
C-reactive protein (mg/L)	3.7	3.9	4.3	5.7*	3.8	5.4
Thyroglobulin (ng/ml)	68				144*	77
Antimicrosomal antibody (U/ml)	159				179	636*

*P<0.05, as compared with base line.

The hematologic and ESR values were normal and did not change, but serum C-reactive protein concentrations increased slightly from 3.7 mg/L at base line to a peak value of 5.7 mg/L 1 week after I-131 therapy.

Serum antimicrosomal antibody concentrations increased from 159 U/ml to 636 U/ml 3 months after therapy.

Conclusion Serum C-reactive protein and thyroglobulin concentrations increase transiently soon after I-131 therapy in patients with hyperthyroidism, indicative of thyroid inflammation. In contrast, serum antithyroid microsomal antibody concentrations increase slowly, indicative of autoimmunization.

COMMENTARY

Serum T_4 and T_3 concentrations may increase slightly during the first week or two after I-131 therapy in patients with hyperthyroidism. There are usually no clinical changes during that interval, but rare patients have symptoms of thyroid inflammation (neck pain and tenderness) or an increase in the clinical manifestations of hyperthyroidism (even thyroid storm) during that interval. Serum thyroglobulin concentrations increase from two- to eight-fold during the first 2 weeks after I-131 therapy (1), more or less consistent with the two-fold rise at 4 weeks reported by Sari et al.

The changes in serum antithyroid microsomal antibody concentrations occurred more slowly, as might be expected if activation of new or preexisting autoimmunity were involved. Serum TSH-receptor antibody concentrations rise to peak values 3 to 12 months after I-131 therapy in patients with Graves' hyperthyroidism, and their production is initiated by I-131 therapy in occasional patients with a toxic nodular goiter.

Serum C-reactive protein concentrations are high in patients with many acute and chronic inflammatory disorders; to the list can be added radiation thyroiditis and some other thyroid disorders. In an extensive survey of 353 patients with different thyroid disorders, high values were found in 76 percent of patients with painful subacute (granulomatous) thyroiditis, 22 percent of women during the hyperthyroid phase of postpartum thyroiditis, and 16 percent of patients taking amiodarone who had hyperthyroidism (iodide-induced, 19 percent; thyroiditis-induced, 12 percent) (2); no patients with Graves' hyperthyroidism or toxic nodular goiter had high concentrations.

As a practical matter, measurements of serum C-reactive protein may be useful in confirming a diagnosis of painful subacute thyroiditis, but whether more useful than measurement of ESR is doubtful. Neither test is useful in distinguishing between the two types of amiodarone-induced hyperthyroidism, for which the correct diagnosis has important implications for therapy.

Robert D. Utiger, M.D.

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Quality of life is not related to current level of thyroid function in patients previously treated for hyperthyroidism caused by Graves' disease

Abraham-Nordling M, Wallin G, Lundell G, Torring O. Thyroid hormone state and quality of life at long-term follow-up after randomized treatment of Graves' disease. Eur J Endocrinol 2007;156:173-9.

SUMMARY

Background Some patients with hyperthyroidism caused by Graves' disease have poor quality of life long after therapy. In this study, quality of life was assessed in patients who had been treated for hyperthyroidism many years ago in relation to their thyroid function at follow-up.

Methods The study subjects were 91 of 179 patients with Graves' hyperthyroidism and little or no ophthalmopathy who had been randomly assigned to treatment with methimazole, radioiodine (I-131), or surgery 14 to 21 years earlier to determine the risk of onset or exacerbation of ophthalmopathy after treatment. Among the 179 patients, 142 participated in this study, and complete responses and test results were available for 91 (64 percent).

These 91 patients (80 women, 11 men) included 38 (42 percent) who had been treated with surgery, 17 (19 percent) with methimazole, 27 (29 percent) with I-131, and 9 (10 percent) with I-131 for persistent or recurrent hyperthyroidism after initial treatment. Each patient completed the Short Form-36, a quality-of-life questionnaire that has Physical and Mental Component scores, each composed of four subscores, and a quality-of-life questionnaire that included questions about well-being. All had measurements of serum thyrotropin (TSH), free thyroxine (T_4), and TSH-receptor (anti-TSH-R) antibodies.

Results The characteristics of the 91 patients and the results of the biochemical studies are shown in the Table.

The mean Physical and Mental Component scores of the Short Form-36 questionnaire were similar in the four treatment groups.

Table. Characteristics and Biochemical Findings in Patients 14 to 21 Years after Initial Treatment for Hyperthyroidism.*

	Surgery (n=38)	Methimazole (n=17)	I-131 (n=27)	Later I-131 (n=9)
Women/men	34/4	14/3	25/2	7/2
Age (yr)	59	61	64	65
Follow-up after initial therapy (yr)	18	18	18	18
T_4 therapy (µg/day)	142	117	142	169
Serum				
TSH (mU/L)	0.9	1.7	0.5	0.3
Free T_4 (ng/dl)	1.5	1.1	1.5	1.5
Anti-TSH-R antibodies (U/L)	7	6	10	8

*Values are means. Reference values: TSH, 0.2 to 4.0 mU/L; free T_4, 0.8 to 1.6 ng/dl; and anti-TSH-receptor antibodies, <8 U/L. To convert serum free T_4 values to pmol/L, multiply by 12.9.

Overall, 44 patients, (48 percent) had normal serum TSH concentrations, 43 (47 percent) low concentrations, and 4 (5 percent) high concentrations. The two component scores were similar in these three groups. The two scores also were similar in the 75 patients (82 percent) who were taking T_4 and the 16 (18 percent) who were not. The scores in all of these subgroups were similar to those in normal subjects.

The only question on the other questionnaire for which results are given is, "Do you feel well now?" Sixty-nine of the 89 patients (78 percent) who answered this question responded "yes," of whom 32 (46 percent) had low serum TSH concentrations. Twenty patients (22 percent) responded "no," of whom 9 (45 percent) had low serum TSH concentrations.

Conclusion In patients with Graves' hyperthyroidism who had been treated years ago, quality of life is normal, and is not related to earlier treatment for hyperthyroidism, present T_4 treatment, or current serum TSH or free T_4 concentrations.

COMMENTARY

The original study of this cohort revealed that I-131 therapy was more likely to be followed by the onset or worsening of ophthalmopathy than either methimazole or thyroidectomy in patients with Graves' hyperthyroidism. There is no mention of ophthalmopathy as a possible cause of poor quality of life in relation to thyroid function in these patients. The two questionnaires described above were actually given to 145 of the original 179 patients (81 percent) 14 to 21 years after initial therapy (1). Analysis of their results revealed decreases in some component scores of the Short Form-36 questionnaire, as compared with normal subjects, and 14 to 38 percent of the patients had persisting unspecified ophthalmologic problems.

This study was limited to the 91 patients who had measurements of serum TSH and free T_4 when they completed the questionnaires. Their Short Form-36 scores were similar to those in age- and sex-matched normal subjects, and did not vary among the four subgroups. Forty-seven percent of the patients had low serum TSH concentrations, and some probably also had high serum free T_4 concentrations, most likely caused by excess T_4 treatment, but possibly also by continued TSH-receptor antibody-mediated thyroid stimulation.

The sensitivity of these questionnaires for detecting changes in quality of life in patients with hyperthyroidism long after initial treatment is probably limited, and the duration of the abnormalities in thyroid function is not known. Nonetheless, it may be reassuring that there seem to be no physical or mental consequences of current mild thyroid dysfunction in patients who had Graves' hyperthyroidism many years ago.

Robert D. Utiger, M.D.

Reference

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Agranulocytosis caused by antithyroid drugs usually occurs within two months after initiation of therapy and lasts less than two weeks

Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. Ann Intern Med 2007;146:657-65.

SUMMARY

Background Agranulocytosis is a well-known adverse effect of antithyroid drugs, but relatively little is known about its timing and duration. This study was done to determine the onset, duration, and other characteristics of agranulocytosis caused by methimazole, carbimazole, and propylthiouracil and other nonchemotherapy drugs.

Methods The study subjects were 973 patients who had agranulocytosis (granulocyte count, $<0.5\times10^9$ cells/L) attributed to many drugs between 1966 and 2006, including 87 patients in whom it was attributed to methimazole, carbimazole, or propylthiouracil. The patients were identified by a systematic review of case reports of drug-related agranulocytosis.

Information was collected about age and sex, concomitant clinical findings, time of onset and duration of agranulocytosis, treatment, and outcome. The likelihood of a relationship between the drug and agranulocytosis was determined by four findings: (1) onset during therapy or within one month after the drug was stopped, (2) the absence of concurrent illness or therapy with other drugs that might cause agranulocytosis, (3) a rise in granulocyte count to $\geq1.5\times10^9$ cells/L within one month after the drug was stopped (with or without therapy with granulocyte- or granulocyte-macrophage colony-stimulating factor [G-CSF, GM-CSF]), and (4) a positive rechallenge test or strong evidence of the causal effect of the drug. The relationship was deemed definite if all 4 criteria were met, probable if criteria 1 to 3 were met, possible if criterion 1 was met and criterion 3 was uncertain, and unlikely if criteria 1 and 2 were not met.

Results Among the 973 patients (mean age, 51 years), agranulocytosis was considered definite in 56 (6 percent), probable in 436 (45 percent), and possible in 481 (49 percent). The patients in the respective groups had received 36, 89, and 55 different drugs. The duration of therapy before the onset of agranulocytosis ranged from 2 to 60 days, and the time from onset to recovery from 4 to 24 days. Other findings: 16 percent of patients had an autoimmune disease, 16 percent had sepsis and 52 percent a nonsystemic infection; 39 percent had hypoplasia and 4 percent hyperplasia of granulocytic cells in the bone marrow; and 24 percent were treated with G-CSF or GM-CSF and 7 percent with glucocorticoids.

With respect to antithyroid drugs, the agranulocytosis was considered probable in 55 patients treated with methimazole, 21 treated with carbimazole, and 10 treated with propylthiouracil, and definite in 1 treated with propylthiouracil. The time to onset and the duration of agranulocytosis were similar for all three drugs (Table).

Table. Median Duration of Therapy before Onset of Agranulocytosis and Duration of Agranulocytosis in Patients Treated with an Antithyroid Drug.

	Methimazole (n=55)	Carbimazole (n=21)	Propylthiouracil (n=11)
Duration of therapy before onset (d)*	42	41	36
Duration of agranulocytosis (d)**	10	8	10

*Granulocyte count $<0.5\times10^9$ cells/L; **Days from onset to $>1.5\times10^9$ cells/L.

The four most common definite or probable causes of agranulocytosis were antiinfective drugs (142 patients), antithyroid drugs (87), psychotropic drugs (85), and antiarrhythmic drugs (39).

Conclusion In patients treated with an antithyroid drug, agranulocytosis is usually detected less than two months after the drug is started and lasts less than two weeks.

COMMENTARY

As a class of drug, antithyroid drugs ranked second in this study, but in another study they ranked first (1). There is obviously reporting bias, and these studies do not provide any information about the number of patients at risk.

What is the frequency of agranulocytosis in patients treated with an antithyroid drug? In the largest study, of 30,798 patients with Graves' hyperthyroidism in whom granulocyte counts were done at regular intervals during therapy, 109 (0.35 percent) had agranulocytosis ($<0.5\times10^9$ cells/L) (2). They included 93 of 26,425 patients (0.35 percent) treated with methimazole and 16 of 4373 (0.36 percent) treated with propylthiouracil. Sixty-seven of the 109 patients (61 percent) were asymptomatic at the time of detection of agranulocytosis, and 34 (31 percent) had no symptoms at any time. The latter finding raises the possibility that some patients have agranulocytosis that resolves despite continued therapy.

The study was done in Japan, but there is no evidence that the risk of antithyroid drug-induced agranulocytosis differs in other ethnic groups. Indeed, about all that is known about risk is that most cases occur soon after the initiation of therapy, as shown in the table, which is when the dose of drug is usually highest.

In this new study, most of the 87 patients treated with an antithyroid drug probably had hyperthyroidism caused by Graves' disease, thereby accounting for a substantial proportion of the 158 patients (16 percent) who had an autoimmune disease. Whether any of the other findings are applicable to antithyroid drugs is not stated.

Robert D. Utiger, M.D.

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The incidence of cancer of several organs is increased in patients with hyperthyroidism treated with radioiodine

Metso S, Auvinen A, Huhtala H, Salmi J, Oksala H, Jaatinen P. Increased cancer incidence after radioiodine treatment for hyperthyroidism. Cancer 2007;109:1972-9.

SUMMARY

Background Patients with hyperthyroidism have been treated with radioiodine (I-131) for many years. One anticipated adverse effect of I-131 was an increased the risk of thyroid or other cancers, and some studies have revealed small increases in the incidence of some cancers. This case–control study was done to determine the long-term risk of cancer, and also recurrent hyperthyroidism and hypothyroidism, in patients with hyperthyroidism treated with I-131.

Methods The study subjects were 2793 patients (2336 women, 457 men; median age, 62 years) with hyperthyroidism who were treated with I-131 between 1965 and 2002 at a single hospital in Finland. The control group consisted of 2793 age- and sex-matched subjects identified in a population database. Patient and treatment information was obtained from hospital records and the Finnish Cancer Registry. The follow-up period started one year after treatment and ended in 2004 or when a patient was found to have cancer or had died. The incidence rates for different cancers were compared in the two groups and in subgroups according to age, dose of I-131, and cause of hyperthyroidism (and their matched control subjects).

Results During a median follow-up period of 10 years, 367 patients and 308 control subjects were found to have one or more cancers. The overall incidence rates were 119 per 10,000 subjects in the I-131-therapy group and 95 per 10,000 subjects in the control group (1 excess case per 418 patients treated with I-131), and the incidence-rate ratio per 10,000 person-years was 1.2 (95 percent confidence interval, 1.1 to 1.5) (Table). The rates in the two groups did not differ until after five years of follow-up.

Among individual cancers, the incidence-rate ratios for cancers of the breast, stomach, kidney, and unspecified primary sites were higher in the I-131 therapy group. The rate ratios for cancer of the thyroid and other organs were similar in the two groups.

Table. Cancer Risk (Incidence Rate-Ratio per 10,000 Person-Years) among Patients with Hyperthyroidism Treated with I-131 and Control Subjects.

	Rate Ratio (95% CI)
All sites	1.2 (1.1–1.5)
Breast	1.5 (1.1–2.2)
Stomach	1.8 (1.0–3.1)
Kidney	2.3 (1.1–5.0)
Unspecified primary sites	2.2 (1.0–4.9)
Thyroid	1.6 (0.6–3.7)

CI denotes confidence interval.

The risk of cancer was increased in patients aged 50 to 59 years (rate ratio, 1.4) and those aged 70 to 98 years (rate ratio, 1.4) at the start of follow-up. The mean total dose of I-131 was 8.2 mCi (303 MBq); 80 percent of the patients were treated once, 16 percent twice, and 4 percent three or more times. The overall risk of cancer increased with increasing dose of I-131.

The rate ratios were similar in the 1604 patients (57 percent) who had Graves' disease and the 1189 (43 percent) who had a toxic nodular goiter (1.2 and 1.3, respectively).

Conclusion The incidence of cancer of the breast, stomach, kidney, and unspecified primary sites is slightly increased in patients with Graves' hyperthyroidism and toxic nodular goiter after I-131 therapy.

COMMENTARY

There have been several large, long-term studies of the incidence of cancer or cancer mortality after I-131 therapy for hyperthyroidism. In this cohort, cancer mortality also was increased (relative risk, 1.3) (1). In other studies, there were small increases, small decreases, or no differences in cancer incidence and mortality in patients treated with I-131, as compared with the general population or matched control subjects (2-5). In all these studies, the standardized incidence ratios or standardized mortality ratios were in the range of 0.8 to 1.5, with one 95 percent confidence interval of 1.0 or very close to it. In some studies, cancer incidence or mortality was increased only in the first years after I-131 therapy, and was not dose-related (3). There were no adjustments for other risk factors for cancer, such as smoking and iodine intake, in these studies.

When present, the excess cancer incidence or mortality was largely in cancers of the thyroid, breast, stomach, and kidneys. These organs have iodine transporters, and therefore concentrate iodide. The thyroid radiation dose is far higher than that of all other organs, but the thyroid is for the most part destroyed, and presumably what is left cannot replicate.

These results, taken together, suggest that I-131 therapy for hyperthyroidism is not associated with an increase in cancer incidence or mortality.

Robert D. Utiger, M.D.

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An antibody that depletes B lymphocytes may induce prolonged remissions in patients with hyperthyroidism caused by Graves' disease

El Fassi D, Nielsen CH, Bonnema SJ, Hasselbalch HC, Hegedus L. B lymphocyte depletion with the monoclonal antibody rituximab in Graves' disease: a controlled pilot study. J Clin Endocrinol Metab 2007;92:1769-72.

SUMMARY

Background The proximate cause of Graves' hyperthyroidism is thyrotropin (TSH) receptor-stimulating antibodies (TRAb). The production of these antibodies is initiated by activation of B lymphocytes and their transformation into antibody-producing plasma cells. B lymphocytes have a unique surface marker, CD20, and administration of the anti-CD20 antibody rituximab results in depletion of these cells and clinical improvement in patients with rheumatoid arthritis and related disorders. This study was done to evaluate the effect of rituximab in patients with Graves' hyperthyroidism.

Methods The study subjects were 20 patients (18 women, 2 men; mean age, 40 years) with Graves' hyperthyroidism, as defined by high serum free thyroxine (T_4) and low serum TSH concentrations, high serum TRAb concentrations (radioreceptor assay; normal, <0.7 IU/L), and diffuse goiter. Ten patients accepted rituximab therapy, and 10 who declined constituted the control group.

The 10 patients in the rituximab group were treated with methimazole for 124 days and with rituximab (375 mg/m^2, intravenously) on days 103, 110, 117, and 124 (three patients received only two doses of rituximab). The 10 patients in the control group were treated with methimazole for 132 days. Serum free T_4 and TRAb were measured before methimazole was started, weekly for six weeks during rituximab therapy, and monthly thereafter (and at the same times in the control group). The primary outcome was recurrent hyperthyroidism after cessation of methimazole.

Results The base-line characteristics of the two groups were similar. All the patients became euthy-roid while taking methimazole. The mean serum TRAb con-centrations in the two groups were similar at base line, when rituximab was started, and when methimazole and rituximab were stopped. The respective mean values were 11.4, 8.3, and 7.3 IU/L in the rituximab group and 12.2, 5.7, and 3.4 IU/L in the control group (P>0.05). The follow-up period after methimazole was stopped was longer in the rituximab group than in the control group (740 vs. 554 days, P<0.02).

One year after methimazole was stopped, 4 patients (40 percent) in the rituximab group remained euthyroid, and they were still euthyroid after 435, 666, 743, and 904 days. In contrast, only 1 patient (10 percent) in the control group was euthyroid at 1 year, and this patient had recurrent hyperthyroidism on day 393.

The duration of methimazole therapy and total dose of methimazole were similar in the rituximab-treated patients who remained euthyroid and those who had recurrent hyperthyroidism. The four patients in the rituximab group who remained euthyroid had serum TRAb concentrations <5.0 IU/L on day 103, when rituximab was started, whereas all five patients in the control group who had similarly low values at that time had recurrent hyperthyroidism.

Five patients had adverse reactions to rituximab, including hypertension, tachycardia, nausea, fever, and chills after the first infusion, which did not recur. Two patients had joint pain and fever after the second infusion, and were withdrawn from the study and treated with glucocorticoids.

Conclusion Rituximab, an antibody that depletes B lymphocytes, may induce more prolonged remissions of Graves' hyperthyroidism in patients with low serum TRAb concentrations during methimazole therapy.

COMMENTARY

Graves' hyperthyroidism is an auto-antibody-dependent disorder. Antigen-presenting cells, including macrophages, dendritic cells, and B lymphocytes, present some form of the TSH-receptor to T-helper (CD4) cells, which produce several cytokines that promote the maturation of B-lymphocytes and their conversion to antibody-producing plasma cells.

Rituximab is a chimeric humanized monoclonal antibody against CD20, a surface protein found on premature and mature B lymphocytes that may function as an ion channel. The antigen-binding (Fab) region is of mouse origin and the effector constant (Fc) region of human origin. Administration of rituximab leads to rapid depletion of peripheral blood and tissue B lymphocytes by apoptosis, antibody-mediated cytotoxicity, and complement-mediated cell lysis, and the depletion persists for four to five months.

There have been two studies of rituximab in patients with Graves' disease, this one in 10 patients with hyperthy-roidism and another in 9 patients with Graves' ophthalmopathy (and 20 treated with intravenous glucocorticoids) (1). Serum TRAb concentrations were similar in the rituximab-treated patients and the control patients in both studies. In this study, the only difference was a lower rate of recurrent hyperthyroidism in patients who had only slightly high serum TRAb concentrations before rituximab was started, and in the other study rituximab was more effective therapy for ophthal-mopathy than were glucocorticoids.

It is possible that rituximab does not alter TRAb production because the antibodies are produced by plasma cells derived from CD20-negative B-lymphocytes, or there is less depletion of CD20-positive B lymphocytes in the thyroid or retroorbital tissues than in the circulation. To explain the clinical benefits described in the two studies, however, other explanations are needed.

Robert D. Utiger, M.D.

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Orbital decompression has long-term benefits in patients with Graves' ophthalmopathy

Jernfors M, Valimaki MJ, Setala K, Malmberg H, Laitinen K, Pitkaranta A. Efficacy and safety of orbital decompression in treatment of thyroid-associated ophthalmopathy: long-term follow-up of 78 patients. Clin Endocrinol (Oxf) 2007;67:101-7.

SUMMARY

Background Graves' ophthalmopathy is characterized by inflammation and enlargement of the extraocular muscles and adipose tissue. One treatment for patients with severe ophthalmopathy is surgical decompression of the orbits. This operation has short-term benefits, but its long-term benefits are less clear. This study was done to determine the long-term benefits of orbital decompression in patients with severe Graves' ophthalmopathy.

Methods From 1985 to 2000, 116 patients with Graves' ophthalmopathy underwent orbital decompression at one hospital in Finland. By 2000, 10 patients had died; of the remaining 106 patients, 78 participated in this study. The patients were asked about their present ophthalmologic status (vision, eye pain, comfort, and appearance), scored on a 10-point visual analogue scale (1, poor; 10, good); the overall benefit of the surgery; and the presence of diplopia before surgery and at the time of follow up. They then underwent ophthalmologic and otolaryngologic examinations.

Results The median age of the 78 patients at the time of surgery was 49 years, and it was 54 years at the time of follow-up; 63 (81 percent) were women and 15 (19 percent) were men. Before surgery, 73 patients (94 percent) had hyperthyroidism, 3 (4 percent) had hypothyroidism, and 2 (2 percent) were euthyroid. All were euthyroid at the time of surgery. At follow-up, 74 were euthyroid, 2 had exogenous hyperthyroidism, and 2 were not tested.

The interval from the onset of ophthalmopathy to surgery was 1.3 years. Sixty-eight patients (87 percent) had been treated with oral glucocorticoids, 55 (70 percent) with intravenous glucocorticoids, and 51 (65 percent) with retrobulbar radiation. The indications for surgery were optic neuropathy in 22 patients (28 percent), proptosis in 37 (48 percent), and severe periorbital and conjunctival inflammation in 19 (24 percent). The operation was transantral decompression in 59 patients (76 percent) and transnasal decompression in 11 (14 percent); 8 patients (10 percent) underwent both operations.

At follow-up (median, 5 years), the median visual analogue score was 7, as compared with 8 in a group of age- and sex-matched normal subjects. The surgery was considered very helpful by 59 patients (76 percent), somewhat helpful by 12 (15 percent), harmful by 2 (3 percent), and of no effect by 5 (6 percent). Both proptosis and intraocular pressure were lower after surgery (Table). Visual acuity improved in 49 percent, did not change in 32 percent, and decreased in 19 percent. The improvements were more frequent and greater in magnitude in the transantral-decompression group. Second operations were of little additional benefit.

Table. Changes in Proptosis and Intraocular Pressure Five Years after Orbital Decompression in 78 Patients with Graves' Ophthalmopathy.*

	Before Surgery	After Surgery	Change
Proptosis (mm)	23	19	–4
Intraocular pressure (mm Hg)	20	16	–4

*Values are means for both eyes.

Fifty-two patients (67 percent) had diplopia before surgery. It improved in 34 (65 percent) and increased in 12 (23 percent) (more in the transantral-decompression group), and 6 (8 percent) had new-onset diplopia after surgery (similar in both groups).

Conclusion Transantral or transnasal decompression results in long-term decreases in proptosis and intraocular pressure and an increase in visual acuity in patients with moderate or severe Graves' ophthalmopathy.

COMMENTARY

There are three treatments for moderate or severe Graves' ophthalmopathy—high doses of oral or intravenous glucocorticoids, retrobulbar radiation, and orbital decompression. The goal of the first two treatments is to reduce extraocular-muscle and retroorbital adipose-tissue inflammation and edema, and that of the third is to enlarge the orbital cavity, so that proptosis and its consequences (decreased retroorbital venous blood flow, corneal exposure, and optic neuropathy) decrease. Transantral decompression is done via a sublabial approach to the maxillary antrum and removal of its bony roof (the floor of the orbit) and the lateral wall of the ethmoid sinus (the medial wall of the orbit), whereas transnasal decompression is done by transnasal ethmoidectomy and removal of the lateral wall of the ethmoid sinus.

Orbital decompression has the greatest and most rapid effect on proptosis and optic neuropathy, retroorbital radiation is least effective but is the safest, and glucocorticoids are in between. In practice, most, if not all, patients with moderate or severe ophthalmopathy are initially treated with glucocorticoids, even if one of the other treatments is to be undertaken immediately.

A more important question concerns the indications for any of these treatments. Few would quarrel with those described by these authors, especially optic neuropathy and severe periorbital and conjunctival edema. Proptosis is an indication for surgery if it is associated with severe periorbital and conjunctival inflammation and edema. Proptosis alone is an indication for surgery for cosmetic reasons.

Transantral decompression is the more effective operation, but the risk of new-onset diplopia is higher. Transnasal decompression is a relatively new operation, and perhaps the results will improve with experience. With respect to follow-up, it seems likely that the 5-year results were better than those soon after surgery, given that the activity of ophthalmopathy tends to subside with time in many patients.

Robert D. Utiger, M.D.

Thyrotropin secretion decreases with age in patients with hypothyroidism

Carle A, Laurberg P, Pedersen IB, Perrild H, Ovesen L, Rasmussen LB, Jorgensen T, Knudsen N. Age modifies the pituitary TSH response to thyroid failure. Thyroid 2007;17:139-44.

SUMMARY

Background Serum thyrotropin (TSH) concentrations increase in response to decreases in thyroid secretion, but the magnitude of the increase varies. In this study, serum TSH and thyroxine (T_4) were measured in patients with hypothyroidism to determine the effect of age as a determinant of TSH secretion.

Methods The study subjects were 578 patients with spontaneous autoimmune hypothyroidism identified from a registry linked to four laboratories in Aarlborg and Copenhagen, Denmark, for the years 1997 to 2000. The laboratories provided measurements of serum TSH, total T_4, and free T_4 to physicians in these two areas. Patients with overt hypothyroidism (high serum TSH and low total or free T_4 concentrations) were identified as possible incident cases. Comprehensive information was obtained from the patients and their physicians.

The diagnosis of hypothyroidism was confirmed if the patients had high serum TSH and low serum total or free T_4 concentrations three or more weeks later or the initially abnormal values were normal after initiation of T_4 treatment. Patients with a history of treatment with any drug that might cause hypothyroidism, thyroid surgery, radioiodine therapy, external radiation of the neck, subacute thyroiditis, or childbirth within the previous year were excluded. More than 99 percent of the patients had high serum antithyroid peroxidase antibody concentrations, and therefore were considered to have autoimmune hypothyroidism.

The patients' serum TSH concentrations were analyzed in relation to their serum total or free T_4 concentrations (measured in 571 and 7 subjects, respectively), age, sex, summer and winter, (1997-2000), and one-year survival.

Results The 578 patients with spontaneous autoimmune hypothyroidism included 460 females (80 percent) and 118 males (20 percent), ranging in age from 2 to 3 days to 99 years. Serum TSH concentrations were highest in the youngest age group, and declined progressively with age ($P<0.01$), whereas serum T_4 concentrations did not change with age (Table).

Table. Serum TSH and Total T_4 Concentrations in Patients with Spontaneous, Overt Autoimmune Hypothyroidism.

Age	No.	Serum TSH (mU/L)	Serum T_4 (μg/dl)*
2 to 3 days–19 years	9	100	3.2
20–39 years	55	70.7	3.2
40–59 years	159	49.5	2.9
60–79 years	231	32.6	3.4
80–99 years	124	24.4	3.7
All	578	39.5	3.2

*Measured in 571 patients. To convert serum T_4 values to nmol/L, multiply by 12.9.

Serum TSH concentrations also were lower as a function of age in the 312 women for whom there was clear evidence of no estrogen therapy or pregnancy. There were no differences in serum TSH concentrations in females and males or summer and winter.

Log serum TSH concentrations were negatively correlated with age, and the negative relationship was not altered by adjustment for one-year survival after diagnosis. Serum TSH concentrations were lower in the older patients when matched according to serum T_4 concentrations, and log serum TSH concentrations were negatively correlated with serum T_4 concentrations.

Conclusion Serum TSH concentrations are lower in relation to serum T_4 concentrations in older patients with spontaneous autoimmune hypothyroidism, suggesting that there is an age-related decline in the sensitivity of the pituitary thyrotrophs to hypothyroidism.

COMMENTARY

Daytime serum TSH concentrations change little with age in normal subjects, nor do serum T_4 concentrations. The clearance of T_4 slows with age. Since serum T_4 concentrations do not change, thyroid secretion must fall. Therefore, 24-hour TSH secretion must fall, probably caused by a decrease in the nocturnal surge of TSH secretion.

The finding of lower serum TSH concentrations in older as compared with younger patients cannot be explained by differences in serum T_4 concentrations. Other explanations include differences in serum free T_4 concentrations, the causes of hypothyroidism, or its rate of onset. Serum free T_4 concentrations, measured in few patients, were probably similarly low in all. The apparent cause of hypothyroidism (autoimmune thyroiditis) in the patients was the same (excepting the few newborn infants), and the rate of onset was probably gradual in all. Another explanation is that older patients secrete TSH that has relatively more biologic activity in relation to its immunologic activity, and therefore measurements of serum immunoreactive TSH underestimates serum TSH biologic activity.

All things considered, the most likely explanation for the difference is a decrease in thyrotroph sensitivity to low serum T_4 concentrations in older people. The consequence of this decrease is less compensation for hypothyroidism. Thyroid secretion will fall more, and so too will triiodothyronine (T_3) secretion relative to that of T_4, because of the relatively greater stimulatory effect of TSH on T_3 synthesis and T_4 deiodination.

One practical consequence of less compensation is that older patients may have more symptoms of hypothyroidism at lower serum TSH concentrations than do younger patients. Another is that their serum TSH concentrations will rise more slowly during antithyroid therapy or after cessation of T_4 therapy

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Thyroxine has beneficial effects in patients with subclinical hypothyroidism

Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver J. The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial. J Clin Endocrinol Metab 2007;92:1715-23.

SUMMARY

Background Subjects with subclinical hypothyroidism may have clinical, physiological, and biochemical findings indicative of hypothyroidism, but whether the findings improve during thyroxine (T_4) therapy is controversial. This study was done to determine the effect of T_4 treatment on these findings in subjects with subclinical hypothyroidism.

Methods The study was a double-blind crossover trial in which 100 subjects with subclinical hypothyroidism (82 women, 18 men; mean age, 54 years) were given 100 μg of T_4 and placebo daily in random order for 12 weeks. All had high serum thyrotropin (TSH) (normal, 0.4 to 4.0 mU/ml) and normal free T_4 concentrations on at least two occasions at least three months apart.

At base line and at the end of each treatment period, quality of life was assessed using the Short Form-36, a general questionnaire that has physical- and mental-component scores, a Hypothyroidism Quality-of-Life questionnaire (18 items), and a Hypothyroid Symptom questionnaire (15 items). Weight, blood pressure, serum TSH, free T_4 and lipids, and flow-mediated dilatation (FMD) of the brachial artery, an indicator of endothelial function, were measured at the same times. The order of T_4 and placebo administration did not affect the results and therefore they were combined.

Results The base-line results were similar in the T_4-first and placebo-first groups; the mean base-line serum TSH concentrations were 5.4 mU/ml (highest, 15.8) in the T_4-first group and 5.3 mU/ml (highest, 13.9) in the placebo-first group. The mean serum TSH concentration was lower and the serum free T_4 concentration was higher at the end of the T_4 period than at the end of the placebo period (Table).

Table. The Effect of T_4 and Placebo Administration on Serum Lipids and Endothelial Function in Subjects with Subclinical Hypothyroidism.

	T_4	Placebo
Serum TSH (mU/L)	0.5	5.2*
Serum free T_4 (ng/dl)	1.6	1.0*
Serum total cholesterol (mg/dl)	220	232*
Serum LDL cholesterol (mg/dl)	131	143*
Brachial-artery flow values		
Base-line flow (ml/min)	58	55
Peak flow (ml/min)	147	143
FMD (%)	5.9	4.2*

To convert serum free T_4 values to pmol/L, multiply by 12.9, and to convert serum cholesterol values to mmol/L, multiply by 0.026.
*P<0.05, between periods.

There was slightly more improvement in the Hypothyroidism Quality-of-Life score and some symptoms of hypothyroidism, and its impact decreased more during T_4 than placebo administration, but few of the differences were statistically significant after correction for multiple comparisons There were no differences in Short Form-36 scores, perceived health status, or treatment satisfaction.

Body weight and blood pressure were similar at the end of each period. The waist–hip ratio was lower after T_4 administration (0.81 vs. 0.83, P<0.01), as were serum total and low-density lipoprotein (LDL) cholesterol concentrations, and the fractional FMD was higher (Table).

Conclusion In subjects with subclinical hypothyroidism, administration of T_4 for 12 weeks, as compared with placebo, results in improvement in some symptoms of hypothyroidism, lower serum total and LDL cholesterol concentrations, and improvement in endothelial function.

COMMENTARY

This study provides additional evidence that there are some short-term benefits of T_4 therapy in subjects with subclinical hypothyroidism. It was not, however, associated with improvement in quality of life, but the duration of therapy was short. An unexpected finding was the small decrease in waist–hip ratio in the T_4-therapy group. The changes in serum lipids were similar to those of other studies, and the study adds useful information about endothelial function.

Regarding T_4 therapy for subjects with subclinical hypothyroidism, it seems reasonable to consider the following issues. Was it detected because the subject had symptoms (case finding), or by screening? How high is the subject's serum TSH concentration, and how long has it been high? What is the likelihood of progression to overt hypothyroidism? Is the presence of a high serum antithyroid antibody concentration an indication for therapy? (In this study 51 percent of the subjects had a high serum antithyroid peroxidase antibody concentration.) Should treatment be based on the presence of other biochemical (serum lipid values) or physiological (endothelial function, cardiac function) abnormalities? T_4 therapy may decrease the subject's symptoms. Subjects with higher serum TSH concentrations and those with high serum antithyroid peroxidase antibody concentrations are more likely to have overt hypothyroidism later. Most if not all of the biochemical and physiological abnormalities are reversible, although whether the improvement is beneficial in the long term is not known.

This study supports the view that people who seek medical care with any symptom(s) that might be attributed to hypothyroidism and are found to have subclinical hypothyroidism should be treated, perhaps for six months, but only if their serum TSH concentrations are high on several occasions and especially if they have a high serum antithyroid peroxidase antibody concentration.

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Thyroid incidentalomas, equally benign and malignant, are occasionally found in patients with head and neck cancer

Nam SY, Roh JL, Kim JS, Lee JH, Choi SH, Kim SY. Focal uptake of 18F-fluorodeoxyglucose by thyroid in patients with nonthyroidal head and neck cancers. Clin Endocrinol (Oxf) 2007;67:135-9.

SUMMARY

Background Many patients with head and neck cancer undergo positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) for staging and monitoring, which may reveal FDG uptake in the thyroid. In this study, the frequency and causes of abnormal FDG-PET uptake by the thyroid were determined in a large group of patients with head and neck cancer.

Methods The study subjects were 689 patients (182 women, 507 men; mean age, 57 years) with biopsy-proven head and neck cancer who underwent FDG-PET imaging before surgical or other treatment. Those with focal thyroid abnormalities underwent computed tomography (CT) of the neck, thyroid ultrasonography, and ultrasound- or palpation-guided fine-needle aspiration of the nodule. Patients with a history of thyroid disease were excluded.

Results Nineteen of the 689 patients (3 percent) had incidental focal thyroid uptake of FDG. They included 11 of the 182 women (6 percent) and 8 of the 507 men (1.6 percent); their mean age was 58 years. Twelve patients were further evaluated, 4 refused further evaluation, and 3 did not return for further studies. Eight of the 12 patients had a squamous-cell carcinoma of the head or neck and 1 each had an adenoid cystic carcinoma, malignant melanoma, myxofibrosarcoma, and undifferentiated carcinoma.

Most of the thyroid nodules appeared as low-attenuation or heterogeneous masses on CT, and they ranged from 0.6 to 3.5 cm (mean, 1.6) in longest dimension. Most were hypoechoic on ultrasonography. The cytologic diagnosis was suspicious for papillary carcinoma in 4 patients; all proved to have papillary carcinoma at surgery. The cytologic diagnosis was follicular tumor in 4; at surgery, 2 proved to have a follicular adenoma, 1 a Hurthle-cell adenoma, and 1 a follicular carcinoma. In the remaining 4 patients, the cytologic diagnosis was hyperplastic nodule; they did not undergo thyroid surgery. Overall, 5 of the 12 patients (42 percent) had a thyroid carcinoma.

The maximum standardized FDG uptake (SUV_{max}), calculated as nodule uptake/(injected dose/lean body weight), ranged from 1.4 to 32.0 in these 12 patients, and the values did not differ significantly in the patients who had a benign nodule and those who had a carcinoma (8.4 vs. 4.2). No combination of imaging results or SUV_{max} values and imaging results distinguished between the benign nodules and carcinomas.

Conclusion Patients with head and neck cancer may have incidental thyroid nodules, as detected by FDG-PET imaging, nearly half of which are thyroid carcinomas.

COMMENTARY

Any examination of the thyroid region, whether by palpation, ultrasonography, radionuclide imaging, MRI, CT, or FDG-PET, will reveal one or more thyroid nodules in some patients. Among these tests, ultrasonography is the most sensitive, but none reliably distinguishes between benign thyroid nodules and thyroid carcinomas.

Most patients undergoing FDG-PET have been patients with nonthyroid carcinomas in whom the test was done for staging or monitoring. Among them, thyroid incidentalomas have been found in 1 to 5 percent. The proportion that were thyroid carcinomas ranged from 15 to 50 percent, higher than in patients with thyroid incidentalomas detected in other ways.

One limitation of FDG-PET of the head and neck is that resolution of the images is not very good, because there may be physiological or nonphysiological uptake by several structures adjacent to the thyroid (lymph nodes, salivary tissue, oropharyngeal tissue). This may be improved by combining FDG-PET with CT. Another limitation applies to identifying thyroid incidentalomas. Both benign nodules and carcinomas may take up FDG (1), and when they do the SUV_{max} values often overlap. For example, among 36 patients who had FDG uptake in a nodule and a cytologic diagnosis of follicular tumor, 15 (42 percent) proved to have a follicular, Hurthle-cell, or papillary carcinoma and 21 (58 percent) a follicular or Hurthle-cell adenoma or a hyperplastic nodule (2).

FDC-PET will no doubt soon be done in most if not all cancer patients at the time of diagnosis, if it is not being done already. Thyroid incidentalomas will be found, and an unusually high percentage of them will be thyroid carcinomas. How far to go in proving that diagnosis, and whether then to advise thyroid surgery, should depend more on the patients' underlying nonthyroid carcinoma, the treatability of the nonthyroid carcinoma, and the patients' prognosis and wishes.

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Few patients with thyroid nodules have high basal or stimulated serum calcitonin concentrations indicative of medullary thyroid carcinoma

Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S, Crocetti U, Attard M, Maranghi M, Torlontano M, Filetti S. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab 2007;92:450-5.

SUMMARY

Background A few thyroid nodules are medullary carcinomas, most of which secrete calcitonin. In this study, serum calcitonin was measured in patients with thyroid nodules, and the results in those patients who had high values were correlated with the pathologic findings in those who underwent surgery.

Methods Basal serum calcitonin was measured in 5817 patients (4706 women, 1111 men; mean age, 50 years) with thyroid nodules. Based on the results of thyroid ultrasonography and measurements of serum free thyroxine, thyrotropin, and antithyroid antibodies, 4894 patients had one or more thyroid nodules, 436 Hashimoto's disease and one or more nodules, 276 an autonomously functioning thyroid adenoma, and 211 a toxic nodular goiter.

Basal serum calcitonin values (normal, ≤10 pg/ml) were categorized as follows: ≤10 pg/ml, negative; >10 to <20 pg/ml, indeterminate; ≥20 to <100 pg/ml, suspicious; and ≥100 pg/ml, strongly suspicious. A pentagastrin stimulation test was done in those with suspicious values; a peak value of >100 pg/ml 2 or 5 minutes after intravenous pentagastrin administration was considered to indicate the presence of medullary carcinoma.

Surgery was recommended for patients whose basal or stimulated serum calcitonin values were >100 pg/ml and those who had biopsy results suggestive of any type of thyroid carcinoma, a functioning thyroid adenoma, or a large goiter. The diagnosis of medullary carcinoma was based on standard histologic criteria and immunostaining for calcitonin, and that of C-cell hyperplasia on the presence of ≥50 calcitonin-positive cells in three low-power fields.

Results The basal serum calcitonin values were ≤10 pg/ml in 5535 of the 5817 patients (95 percent). Among the other 282 patients (5 percent), most had values of >10 to <20 pg/ml (indeterminate) (Table).

Table. Diagnoses of Medullary Carcinoma or C-Cell Hyperplasia in Patients with High Basal Serum Calcitonin Concentrations.

Basal Serum Calcitonin (pg/ml)	No. of Patients	Pentagastrin Test (No. Positive/ No. Tested)	Histology (No. Medullary Carcinoma/No. C-Cell Hyperplasia)
Total	282 (5%)	17/273	15/7
>10 to <20	216 (4%)	1/216	0/1
≥20 to <100	57 (1%)	16*/57	6/6
≥100	9 (0.2%)	NT**	9/0

*Two patients with positive pentagastrin-stimulation tests declined surgery. They had no change in clinical findings or basal or stimulated serum calcitonin values during follow-up.
**Not tested.

Surgery was advised for 26 patients on the basis of their serum calcitonin values. All 9 patients with basal values ≥100 pg/ml had medullary carcinoma. Among the 17 patients who had stimulated values >100 pg/ml, 6 had medullary carcinoma, 7 C-cell hyperplasia, 2 no C-cell abnormality, and 2 were not operated on. Overall, 15 patients (0.3 percent) had medullary carcinoma and 7 (0.1 percent) C-cell hyperplasia. Four carcinomas were <1 cm in longest dimension.

None of the 723 patients with normal basal serum calcitonin values who underwent thyroid surgery for other reasons had medullary carcinoma or C-cell hyperplasia.

Conclusion Few patients with thyroid nodules have medullary carcinoma or C-cell hyperplasia, but among them, high basal or pentagastrin-stimulated serum calcitonin values are sensitive and specific indicators of these two disorders.

COMMENTARY

The European Thyroid Association recommends that serum calcitonin be measured in patients with thyroid nodules, while the American Thyroid Association (ATA) does not take a position for or against this test. In a survey of ATA members, less than 5 percent routinely ordered the test in these patients. One reason for the lack of enthusiasm for the test here is that pentagastrin is not available. In the strongest study supporting serum-calcitonin screening, 44 (0.4 percent) of 10,864 patients with thyroid nodules had high basal serum calcitonin values (1). All also had high pentagastrin-stimulated serum calcitonin values, and all had medullary carcinoma. The results of similar studies are less compelling, in terms of the frequency of high basal and high pentagastrin-stimulated values.

Medullary thyroid carcinoma is rare, and the number of cases reported in screening programs is excessive. If approximately 30 percent of people in the United States population have thyroid nodules, and 0.25 percent of the patients with nodules have high basal serum calcitonin values, then one would expect more than 200,000 cases of medullary carcinoma, far higher than the true prevalence.

Costante et al. extend the debate for and against screening, and their study emphasizes the utility of pentagastrin testing. While all 9 patients with basal serum calcitonin values ≥100 pg/ml had medullary carcinoma, only 17 (6 percent) of the 273 patients with basal values ≥10 to <100 pg/ml had positive pentagastrin tests and only 6 (2 percent) of them had medullary carcinoma. Pentagastrin testing is unpleasant, but these data argue that it is an essential part of screening to avoid unnecessary surgery. Unless it becomes available again in the U.S., we should be cautious about endorsing serum-calcitonin screening.

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Metastases of nonthyroid carcinomas are a rare cause of thyroid nodules

Papi G, Fadda G, Corsello MM, Corrado S, Rossi ED, Radighieri E, Miraglia A, Carani C, Pontecorvi A. Metastases to the thyroid gland: prevalence, clinicopathologic aspects and prognosis: a 10-year experience. Clin Endocrinol (Oxf) 2007;66: 565-71.

SUMMARY

Background Few thyroid nodules are carcinomas, and among the latter few are metastases of carcinomas arising in other organs. Nonetheless, the possibility that a thyroid nodule is a metastasis should be kept in mind, especially if the cytologic features of the nodule are not clear. This study was done to determine the frequency of metastases to the thyroid in patients with nonthyroid carcinomas and the prognosis of the patients.

Methods Patients with thyroid metastases were identified from the databases of two centers in Italy. Their records, cytology, and, if thyroid surgery was done, histology were reviewed. The histologic sections were stained with antibodies to thyroglobulin, thyroid transcription factor-1, and calcitonin, and, as suggested by the histologic findings, antibodies to antigens found in nonthyroid carcinomas, for example, CD10 for renal-cell carcinoma, and chromogranin A for neuroendocrine carcinomas.

Results During the study period, 18,105 thyroid operations were done; 2111 (12 percent) revealed a carcinoma or other malignant tumor, of which 24 (1 percent) were nonthyroid carcinomas. During the same interval, 29,708 fine-needle aspirations were done; 1633 (5 percent) revealed a carcinoma, of which 22 (1 percent) were nonthyroid carcinomas. The nonthyroid carcinomas constituted 0.1 percent of all histologic diagnoses and also 0.1 percent of all the cytologic diagnoses. Overall, 36 patients had thyroid metastases, of whom 21 underwent partial or total thyroidectomy.

The 36 patients with thyroid metastases of a nonthyroid carcinoma included 19 women (53 percent) and 17 men (47 percent), and their mean age was 65 years. The metastases (all were single) were palpable in 26 of the patients (72 percent) and were detected by an imaging procedure in 10 (28 percent). Five of the patients (14 percent) had only thyroid metastases and 31 (86 percent) had metastases in other organs. On ultrasonography, all the thyroid metastases were hypoechoic and had ill-defined margins.

Among the 36 patients with thyroid metastases, 9 (25 percent) had lung cancer, 5 (14 percent) esophageal cancer, 5 (14 percent) breast cancer, 5 (14 percent) renal-cell cancer, 4 (11 percent) laryngeal cancer, 3 (8 percent) colon cancer, 2 (6 percent) skin cancer, 1 (3 percent) cancer of the urinary bladder, and 2 (6 percent) cancer of unknown primary site.

The mean time from diagnosis of the primary tumor to diagnosis of the thyroid metastases was 25 months in the 21 patients who underwent thyroid surgery and 20 months in the 15 patients who did not (overall range, 1 month to 13 years). The patients with thyroid metastases were followed for from 2 months to 13 years. Overall, 7 of the 36 patients (19 percent) survived more than 5 years, and 4 were still alive at the end of the study (3 had only thyroid metastases).

Conclusion Carcinomas in the thyroid gland are rarely metastases of nonthyroid carcinomas. When present, they are most likely to be metastases of carcinomas of the lungs, esophagus, breast, or kidneys. Some of the patients survive a long time, especially those who have metastases only to the thyroid gland.

COMMENTARY

It should come as no surprise that the frequency of thyroid metastases in patients with nonthyroid carcinoma is higher when the thyroid is examined at autopsy, approximately 3 to 5 percent, than in clinical studies like this. The difference is likely to narrow as more imaging studies are done in patients with carcinoma and more nodules in the thyroid are biopsied.

When should the possibility that a thyroid nodule is a metastasis of a nonthyroid carcinoma be considered? One possibility is in patients known to have a nonthyroid carcinoma, but if they have high-stage disease proving that the nodule is a metastasis may not be necessary. Ultrasonography will not help, because the features described are those of many thyroid nodules. All the patients in this study were known to have a nonthyroid carcinoma at the time the thyroid metastasis was detected, but that is not always true. In other studies, the thyroid metastasis was the first manifestation of the nonthyroid carcinoma in 5 of 15 patients (33 percent) (1) or was detected by palpation or imaging at the time of initial evaluation in 8 of 20 patients (40 percent) (2). Another possibility is that the results of fine-needle-aspiration cytology are not consistent with either a benign thyroid nodule or papillary or medullary carcinoma of the thyroid. Positive immunostaining for thyroglobulin and calcitonin should confirm that the nodule is of thyroid follicular-cell or C-cell origin, but poorly differentiated thyroid carcinomas and anaplastic carcinomas rarely contain thyroglobulin. Immunostaining for other substances should identify the tissue of origin of the nonthyroid carcinoma.

Robert D. Utiger, M.D.

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Ethanol injection is an effective treatment of thyroid-bed and cervical lymph-node recurrences in patients with papillary carcinoma

Lim CY, Yun JS, Lee J, Nam KH, Chung WY, Park CS. Percutaneous ethanol injection therapy for locally recurrent papillary thyroid carcinoma. Thyroid 2007;17:347-50.

SUMMARY

Background The most common sites of recurrence of papillary carcinoma of the thyroid are in the bed of the thyroid and cervical lymph nodes. In this study, the efficacy of ethanol injection as treatment for these local recurrences in patients with papillary carcinoma was evaluated.

Methods Sixteen patients (13 women, 3 men; mean age, 66 years) with recurrent papillary carcinoma in the thyroid bed or cervical lymph nodes were studied. They had been treated by total thyroidectomy and central neck dissection, and then with radioiodine (I-131) and thyroxine. Six were not considered candidates for reoperation because of co-morbidity and 10 refused reoperation. The sites of carcinoma were identified by ultrasonography and ultrasound-guided fine-needle aspiration cytology.

The treatment consisted of inserting a fine needle into the tumor nodule with ultrasound guidance and slowly injecting 99 percent ethanol until the echogenicity of the nodule decreased. If leakage of ethanol outside the nodule was seen or the patient had severe pain, the injection was stopped. Ultrasonography and ultrasound-guided fine-needle aspiration were repeated at three-month intervals. Treatment was considered successful if the nodule disappeared, tumor cells were not seen if the nodule was aspirated, or the nodule had decreased by >50 percent in size and did not enlarge again on follow-up ultrasonography even if cancer cells were seen in the last aspirate.

Results The 16 patients had 24 nodules of recurrent carcinoma; 8 in the thyroid bed, 3 in the central lymph-node compartment, and 13 in lateral lymph node compartments (Table). Eight nodules were injected once, 18 twice, 2 three times, and 1 four times (mean, 2). The mean volume of ethanol injected was 1.1 ml (range, 0.3 to 3.3). The mean follow-up period was 24 months (range, 13 to 43).

Table. Mean (Range) Changes in Nodule Size after Ethanol Injections in 16 Patients with Recurrent Papillary Carcinoma.

	No.	Before	After
All nodules (mm)	24	10 (6-29)	5 (0-17)
Thyroid bed (mm)	8	12 (5-21)	6 (0-14)
Lymph nodes (mm)	16	8 (6-29)	5 (0-20)

The changes in mean nodule size also are shown in the Table. Twenty nodules (83 percent) decreased in size and four (17 percent) disappeared after an average of two injections. Among the 20 nodules, follow-up aspiration cytology revealed no tumor cells in 5 nodules and tumor cells in 15 nodules that had initially decreased by >50 percent and did not enlarge later.

All the patients had mild pain at the injection sites that lasted less than 24 hours, and one patient was hoarse for five days.

Conclusion In patients with papillary carcinoma who have recurrent tumor in the thyroid bed or cervical lymph nodes, injections of ethanol reduce the size of the tumor and may completely destroy it, and have few adverse effects.

COMMENTARY

Most patients with papillary carcinoma have an excellent prognosis. The most common sites of recurrence are in the thyroid bed or cervical lymph nodes. Patients with recurrences are often treated by surgery, external-beam radiation, or radioiodine. Surgery is difficult, because the patients have had one or more operations, the recurrences may be hard to identify, and the risk of injury to other structures in the neck is substantial. Radiation therapy causes inflammation and scarring of these same structures. Radioiodine therapy may not be effective, because the tumor nodules often do not concentrate iodine, and the radiation carries its own risks, particularly in patients given high cumulative doses.

Ultrasound-guided percutaneous ethanol injection has been used to treat patients with nodules of papillary carcinoma in the thyroid bed and cervical lymph nodes, with success and few adverse effects (1,2). This study by Lim et al. provides further evidence for the efficacy and safety of ethanol injections to treat these patients. They found that one to four injections of ethanol resulted in a decrease in the size and sometimes complete destruction of the nodules, whether in the thyroid bed or lymph nodes. There was no evidence of regrowth of any nodule that had been injected.

Ethanol-injection treatment should be offered only to patients in whom tumor recurrence has been documented by fine-needle aspiration biopsy. The efficacy and safety of this treatment (and radiofrequency ablation [2]) in destroying recurrent tumor nodules is clear. However, several questions remain. Should all patients with recurrent tumor nodules in the neck be treated? Should ethanol ablation be offered as soon as a tumor nodule is detected, no matter what its size? Most important, does treatment—by any of these methods—improve quality of life or increase longevity?

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Quantitative measurements of thyroid blood flow are useful in differentiating between thyroiditis and Graves' disease as causes of hyperthyroidism

Ota H, Amino N, Morita S, Kobayashi K, Kubota S, Fukata S, Kamiyama N, Miyauchi A. Quantitative measurement of thyroid blood flow for differentiation of painless thyroiditis from Graves' disease. Clin Endocrinol (Oxf) 2007;67:41-5.

SUMMARY

Background There are two types of subacute thyroiditis—painless (silent) thyroiditis (including postpartum thyroiditis) and subacute (painful) thyroiditis. Distinguishing between thyroiditis, particularly painless thyroiditis, and hyperthyroidism caused by Graves' disease is important, because their course and treatment are different. In this study, quantitative measurement of thyroid blood flow by ultrasonography was evaluated as a test for the differential diagnosis of thyroiditis and Graves' disease.

Methods The study subjects were 114 patients with hyperthyroidism and 25 normal subjects. All the patients had high serum free thyroxine (T_4) and low serum thyrotropin (TSH) concentrations when first seen. Fifty-six (49 percent) had Graves' disease, as defined by hyperthyroidism and high serum TSH-binding inhibitory antibody (TBII) values, measured by radioreceptor assay (normal, <15 percent inhibition of TSH binding) or high thyroid radioiodine (I-131) uptake. Twenty-eight (24 percent) had painless thyroiditis, defined as hyperthyroidism for less than three months and a low thyroid I-131 uptake. Thirty (26 percent) had subacute painful thyroiditis, defined as hyperthyroidism, neck pain and tenderness, fever, high serum C-reactive protein concentrations, low thyroid I-131 uptake, and hypoechogenicity on ultrasonography. The diagnosis of painless or subacute painful thyroiditis was confirmed by the spontaneous disappearance of symptoms and of high serum free T_4 concentrations.

Thyroid volume and blood flow were measured by ultrasonography. The latter involved measurement of dynamic blood flow by gray-scale power Doppler ultrasonography in several regions within the thyroid gland, and then calculation of the number of pixels of blood flow and the total number of pixels in those regions. The results were expressed as the ratio of the former to the latter, expressed as a percentage.

Results The characteristics of the four groups, their standard test results, and the results of the quantitative measurements of thyroid blood flow are shown in the Table.

Table. Demographic Characteristics and Mean Thyroid Test Results in 114 Patients with Hyperthyroidism and 25 Normal Subjects.

	Graves' Disease (n=56)	Painless Thyroiditis (n=28)	Subacute Thyroiditis (n=30)	Normal Subjects (n=25)
Women/men	45/11	22/6	24/6	20/5
Age (yrs)	41	43	50	40
Serum free T_4 (ng/dl)	3.2*	2.0*	2.6*	1.0
Serum TBII (%)	72.3*	9.8*	6.8	5.2
3-hr thyroid I-131 uptake (%)	29**	5	4	ND
24-hr thyroid I-131 uptake (%)	40**	1	2	ND
Thyroid volume (ml)	34*	21*	23*	13
Thyroid blood flow (%)	15*	0.8	0.9	0.8

*P<0.01, as compared with the normal subjects; and P<0.01, as compared with the two groups of patients with thyroiditis. ND, not done.
To convert serum free T_4 values to pmol/L, multiply by 12.9.

All patients with Graves' hyperthyroidism had thyroid blood flow values >4 percent and serum TBII values ≥15 percent. All patients with painless thyroiditis and subacute thyroiditis had thyroid blood flow values <4 percent.

Conclusion Among patients with hyperthyroidism, painless thyroiditis and subacute thyroiditis can be distinguished from Graves' disease by quantitation of thyroid blood flow by ultrasonography.

COMMENTARY

Strictly speaking, thyroiditis causes thyrotoxicosis, defined as toxic effects of T_4 in tissues, due to excess release of stored T_4, but not hyperthyroidism, defined as excess thyroid hormone synthesis, manifested clinically by high thyroid radioiodine uptake. Graves' disease causes both hyperthyroidism and thyrotoxicosis.

Subacute painful thyroiditis is characterized by thyroid pain and tenderness and nonspecific symptoms of mild systemic illness, rather than of thyrotoxicosis. The diagnosis can be confirmed by a high red-cell sedimentation rate or serum C-reactive protein value (see p. 26), but neither these measurements nor other diagnostic studies are usually needed. The more difficult distinction is between painless thyroiditis and Graves' hyperthyroidism, but here, too, further diagnostic studies are usually not needed. Patients with painless thyroiditis have fewer symptoms (for shorter durations) and smaller goiters than do patients with Graves' hyperthyroidism, and no ophthalmopathy. If there is uncertainty, and the thyrotoxicosis is mild, then watchful waiting is quite appropriate.

If more tests are needed, there are four choices. (1) Measurement of the ratio of serum total T_3 (ng/dl) to total T_4 (μg/dl), which is usually >20 ng/μg in patients with Graves' hyperthyroidism and lower in patients with thyroiditis (the ratios of serum free T_3 to free T_4 overlap more in the two groups). These measurements may already be available, and if not they take a few hours to a day. (2) Measurement of radioiodine uptake, which as reported by Ota et al., can be done in 3 hours instead of the usual 24 hours. (3) Measurement of serum TBII, which takes a good deal longer. (4) Thyroid ultrasonography, with measurements of thyroid volume and blood flow (there is hypoechogenicity in all three disorders), which also can be done quickly. If the serum total T_3 to total T_4 ratio is not definitely high or low, and uncertainty persists after watchful waiting, any of the other three tests can be done then.

Robert D. Utiger, M.D.

Some patients with autoimmune thyroid disease have high serum titers of antipituitary antibodies and growth hormone deficiency

Manetti L, Lupi I, Morselli LL, Albertini S, Cosottini M, Grasso L, Genovesi M, Pinna G, Mariotti S, Bogazzi F, Bartalena L, Martino E. Prevalence and functional significance of antipituitary antibodies in patients with autoimmune and non-autoimmune thyroid diseases. J Clin Endocrinol Metab 2007;21:2176-81.

SUMMARY

Background Some patients with Hashimoto's disease or Graves' disease have high serum concentrations of antipituitary antibodies. In this study, these antibodies were measured in large numbers of patients with both autoimmune thyroid diseases, and pituitary function was assessed in those who had high serum titers of the antibodies.

Methods Serum antipituitary antibodies were measured in 135 normal subjects (111 women, 24 men), and 1290 patients (1099 women, 191 men) with thyroid disorders. They included 961 patients with autoimmune thyroid disease (707 with Hashimoto's thyroiditis and 254 patients with Graves' hyperthyroidism), 60 with toxic nodular goiter, and 269 with nontoxic nodular goiter. The mean age in the five groups ranged from 38 to 53 years. From 37 to 87 percent of the patients in the four groups were taking thyroxine or methimazole and were euthyroid.

Antipituitary antibodies were measured by immunofluorescence using anterior and posterior pituitary tissue from young baboons and serum diluted 1:10. The tests were considered positive if there was diffuse cytoplasmic staining, and the serum was diluted 1:30 and 1:90 and tested again. Pituitary function was tested in those patients who had a high serum titer of antipituitary antibodies, and pituitary MRI was done in those who had abnormal pituitary function. Serum anti-21-hydroylase, glutamic acid decarboxylase, antiparietal cell, and transglutaminase antibodies also were measured.

Table. Serum Antipituitary Antibody Titers in Patients with Thyroid Disorders and Normal Subjects.

	Negative	Titer 1:10	Titer 1:30	Titer 1:90
Hashimoto's disease	615 (87%)	66 (9%)	18 (3%)	8 (1%)
Graves' disease	236 (93%)	14 (6%)	3 (1%)	1 (0.4%)
Toxic nodular goiter	60 (100%)			
Nontoxic nodular goiter	266 (99%)	3 (1%)		
Normal subjects	135 (100%)			

Results Antipituitary antibodies were not detected in the serum of any normal subject, but were detected in some pateints with Hashimoto's disease and Graves' disease and a few patients with a nodular goiter (Table).

Among the 110 patients with autoimmune thyroid disease who had positive serum antipituitary antibody tests, 50 (45 percent) had high titers of both anti-anterior pituitary and anti-posterior pituitary antibodies, 49 (45 percent) had a high titer of anti-anterior pituitary antibodies, and 11 (10 percent) had a high titer of anti-posterior pituitary antibodies. There was no difference in the frequency of high serum titers of these antibodies in patients with hypothyroidism or hyperthyroidism and those who were euthyroid. One hundred (10 percent) of the patients with autoimmune thyroid disease had one or more other autoimmune disorders.

Pituitary function was assessed in 102 of the patients with high serum titers of antipituitary antibodies. Thirty-six (35 percent) had growth hormone deficiency, as defined by a low serum growth hormone response to growth hormone releasing-hormone-arginine stimulation; they included 6 of the 9 patients (66 percent) with a 1:90 titer of serum antipituitary antibodies, 10 of 19 (53 percent) who had a 1:30 titer, and 20 of 74 (27 percent) who had a 1:10 titer. No other anterior pituitary hormone deficiencies were found. One patient had diabetes insipidus. Pituitary MR imaging, done in all 36 patients with growth hormone deficiency, was abnormal in 21 (58 percent); the abnormalities were thickening of the pituitary stalk in 11 patients, an empty sella turcica in 8, and an enlarged pituitary gland in 2.

Conclusion More patients with Hashimoto's thyroiditis or Graves' disease have high serum titers of antipituitary antibodies than do patients with multinodular goiter or normal subjects. Patients with these antibodies may have growth hormone deficiency and anatomic abnormalities of the pituitary gland.

COMMENTARY

Autoimmune polyendocrine syndromes types 1 and 2 are well-defined entities. Patients with autoimmune thyroid disease and other autoimmune disorders, such as autoimmune pituitary disease, but excluding autoimmune adrenal insufficiency, hypoparathyroidism, and candidiasis, have been categorized as having autoimmune polyglandular syndrome type 3. In six similar studies cited by Manetti et al., from 9 to 56 percent of patients with Hashimoto's disease, 7 to 64 percent of patients with Graves' disease, and 0 to 9 percent of normal subjects had high serum titers of antipituitary antibodies, lending credence to the existence of a type 3 autoimmune polyglandular syndrome.

Many autoimmune endocrine disorders are defined by the presence of high serum titers or concentrations of anti-organ antibodies, and to a lesser extent by structural or functional abnormalities. Not only do more patients have the antibodies than have endocrine dysfunction, but the functional role of the antibodies and the antigens recognized by them are usually not known. These statements certainly apply to antipituitary antibodies. Some of the antibodies may destroy pituitary tissue in its entirely, given the presence of an empty sella turcica in some patients, but on the other hand why was growth hormone deficiency the only abnormality of pituitary function despite diffuse pituitary immunostaining?

Robert D. Utiger, M.D.

Hypothyroxinemia in pregnant women has few deleterious effects on the outcomes of pregnancy or on perinatal morbidity

Casey BM, Dashe JS, Spong CY, McIntire DD, Leveno KJ, Cunningham FG. Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. Obstet Gynecol 2007;109:1129-35.

SUMMARY

Background Pregnant women who have subclinical hypothyroidism (high serum thyrotropin [TSH] and normal free thyroxine [T_4] concentrations) during the first half of pregnancy have an increased risk of preterm delivery and other adverse outcomes of pregnancy, and the neurodevelopment of their offspring may be impaired. The neurodevelopment of the offspring of pregnant women who have low serum free T_4 concentrations but normal serum TSH concentrations (hypothyroxinemia) may also be impaired. This study was done to determine whether the risk of adverse outcomes of pregnancy and perinatal morbidity were increased in pregnant women with hypothyroxinemia.

Methods Serum TSH and free T_4 were measured during the first 20 weeks of gestation in 17,298 women with a singleton pregnancy. The women were given a diagnosis of hypothyroxinemia if they had normal serum TSH and low free T_4 concentrations, and subclinical hypothyroidism if they had high serum TSH and normal serum free T_4 concentrations. The reference range for serum TSH was 0.08 to 3.0 mU/ml, which was derived from the 2.5 and 97.5 percentiles of the gestational age–specific values in this cohort. The reference range for serum free T_4, derived in the same way, was 0.86 to 1.9 ng/dl (11 to 24 pmol/L).

Information about the outcomes of pregnancy was obtained from the hospital's perinatal and infant-outcome databases. Gestational hypertension was defined as blood pressure ≥140/90 mm Hg. Severe preeclampsia was defined as one or more of the following: persistent headache, blood pressure >160/110 mm Hg, serum creatinine >1.0 mg/dl (88 μmol/L), serum aspartate aminotransferase at least twice the upper limit of normal, thrombocytopenia, or proteinuria.

Results Among the 17,298 women, 233 (1 percent) had hypothyroxinemia and 598 (3 percent) had subclinical hypothyroidism. The women with hypothyroxinemia and those with subclinical hypothyroidism differed from the women with normal serum TSH and free T_4 concentrations in several ways (Table 1).

Table 1. Characteristics and Outcomes in Pregnant Women with Hypothyroxinemia, Normal Thyroid Function, and Subclinical Hypothyroidism.

	Hypothyroxinemia (n=233)	Normal (n=16,011)*	Subclinical Hypothyroidism (n=598)
Age (yr)	28**	26	27**
Multiparous	165 (71%)**	10,235 (64%)	374 (62%)
Weight (lb)	178**	171	176**
Body–mass index (kg/m^2)	33	32	32
Gestational hypertension	18 (8%)	1422 (9 %)	56 (9%)
Severe preeclampsia	10 (4%)	851 (5%)	36 (6%)
Placental abruption	1 (0.4%)	50 (0.3%)	5 (0.8%)**

*Complete data were not available for all 17,298 normal women.
**P≤0.05, as compared with normal women

There were no differences in the frequency of preterm delivery in the three groups, except that delivery at 34 weeks of gestation or less was more common in the women with subclinical hypothyroidism (4 vs. 2 and 2.5 percent). The frequency of birth weight ≤1000, ≤2500, and ≥4000 g was similar in the three groups. Among the perinatal outcomes (Table 2), intraventricular hemorrhage was more common in the infants of women with hypothyroxinemia, and the respiratory distress syndrome was more common in the infants of women with subclinical hypothyroidism.

Table 2. Neonatal Outcomes in Women with Hypothyroxinemia, Normal Thyroid Function, and Subclinical Hypothyroidism.

	Hypothyroxinemia (n=233)	Normal (n=16,011)	Subclinical Hypothyroidism (n=598)
Admission to intensive care	3 (1.3%)	360 (2%)	24 (4%)*
Respiratory distress syndrome	3 (1.3%)	243 (1.5%)	15 (2%)*
Intraventricular hemorrhage	1 (0.4%)*	11 (0.1%)	1 (0.2%)
Major malformations	1 (0.4%)	181 (1.1%)	6 (1.0%)
Fetal and neonatal deaths	0 (0%)	118 (0.7%)	9 (1.5%)

*P≤0.05, as compared with normal women.

Conclusion The frequency of adverse outcomes of pregnancy and perinatal morbidity are slightly higher among women who have subclinical hypothyroidism than among those who have hypothyroxinemia during the first 20 weeks of gestation.

COMMENTARY

Neither subclinical hypothyroidism nor hypothyroxinemia in these pregnant women was associated with many adverse outcomes of pregnancy or perinatal morbidity, but overall the effects of subclinical hypothyroidism were slightly greater. The changes in thyroid function in the two groups were by definition different, and they were more indicative of thyroid dysfunction and disease in the women with subclinical hypothyroidism.

These findings have led to calls for screening all pregnant women for thyroid dysfunction. That seems premature. These were small studies in which serum TSH, freeT_4, or both was measured only once. With respect to screening, the important questions are what should be measured; when should the measurements be done; and whether any abnormality should be confirmed before treatment is initiated.

An even more important question is whether T_4 treatment of pregnant women with hypothyroxinemia or subclinical hypothyroidism benefits either the women or their offspring during gestation or later. Some would answer that the offspring do benefit, based on the benefits of iodide supplementation in pregnant women and fetuses with iodide deficiency, but the relevance of these results to pregnant women with subclinical hypothyroidism or hypothyroxinema whose fetuses have normal thyroid function is not clear.

Robert D. Utiger, M.D.

MEETING-AT-A-GLANCE

AMERICAN THYROID ASSOCIATION

78th Annual Meeting of the American Thyroid Association

Sheraton New York Hotel & Towers • New York, NY • October 3 – 7, 2007

Time	Wednesday 10/3/07	Thursday 10/4/07	Friday 10/5/07	Saturday 10/6/07	Sunday 10/7/07
6:00	Exhibitors Move-In 8:00 - Noon	Early Risers	Early Risers	Early Risers	
7:00	Endocrine Fellows Conference 6:45 am - 3:45 pm	CME Symposium 6:30 - 7:45 am	CME Symposium 6:30 - 7:45 am	CME Symposium 6:30 - 7:45 am	
8:00		Welcome : 8:00 - 8:15 am Keynote Speaker: 8:15 am - 9:00 am	Paul Starr Lecture: 8:00 - 8:45 am Simultaneous Symposia: 8:45 - 10:00 am Thyroid Grand Rounds | Translational	Van Meter Lecture: 8:00 - 8:45 am Simultaneous Symposia: 8:45 - 10:00 am Pediatric Thyroidology | Autoimmunity	Plenary: Oral Abstracts: 8:00 - 9:00 am Simultaneous Symposia: 9:00 - 10:15 am Clinical | Translational
9:00	ATA Board of Directors Meeting 7:30 - 1:00 pm	Plenary: 4 Oral Abstracts 9:00 - 10:00 am			
10:00	Registration Open: 10:00 am - 9:00 pm	Exhibit Hall Open: 9:00 am - 3:45 pm Break in Exhibit Hall: 10:00 - 10:30 am	Exhibit Hall Open: 9:00 am - 3:15 pm Break in Exhibit Hall: 10:00 - 10:30 am	Exhibit Hall Open: 9:00 am - 1:00 pm Break: 10:00 - 10:30 am	Refreshment Break: 10:15 - 10:30 am
10:30			Simultaneous Symposia: 10:30 - 11:45 am Arthur Bauman Clinical Symposium | Translational	Short Calls 6 Oral Abstracts: 10:30 - Noon	Translational Symposium 10:30 am - Noon
11:00		Translational Symposium 10:30 - 11:45 am			
12:00	ATA Committees & Board Liaisons Noon - 2:00	Poster & Exhibit Review 11:45 am - 12:45 pm	Poster & Exhibit Review Noon - 1:00 pm	Poster & Exhibit Review Noon - 1:00 pm	78th ATA Annual Meeting Ends at Noon
1:00	Advanced Ultrasound Symposium *(Requires Pre-Registration)* 1:00 - 5:00 pm	Meet the Professor Workshops 12:45 - 1:45 pm Thyroid Disease & Reproduction-***Margaret Wierman*** Thyroid Disease in Older Adults-***Kathryn Schuff*** Euthyroid Sick Syndrome Update-***Jonathan Lo Presti*** Nuclear Cofactors-***Ronald Cohen*** Proteomic Profiling-***Richard Robbins*** Thyroid Hormone Transport by MCT8-***Alexandra Dumitrescu***	Meet the Professor Workshops 1:00 - 2:00 pm Ultrasound Evaluation of the Postoperative Neck-***Jill Langer*** Pediatric Thyroid Cancer-***Steve Waguespack*** Graves' Orbitopathy-***Mike Kazim*** TRalpha in adipocyte Development-***Sheue-yann Cheng*** Perchlorate and Other Environmental Disrupters-***Gregory Brent*** DIO2 knockout-***Valerie Galton***	Meet the Professor Workshops 1:00 - 2:00 pm Thyroid Disease and the Brain-***Mary Samuels*** Thyroid Emergencies-***Victor Bernet*** Radioactive Iodine and the Salivary Glands-***Louis Mandel*** The Role of CoRepressors in TH action-***Tony Hollenberg*** Technical Aspects of Measuring Iodide-***Sam Pino*** TR Action and STORMs-***John Baxter***	
1:30	Exhibit Hall open 1:00-5:00 pm				
2:00		Oral Abstract (6) Sessions: 1:45 - 3:15 pm Clinical | Basic	Ingbar Award Lecture 2:00 - 2:45 pm	Abbott State of Art 2:00 - 2:45 pm	
3:00		Poster Review & Break: 3:15 - 3:45 pm	Poster Review & Break: 2:45 - 3:15 pm	Break: 2:45 - 3:15 pm	
3:30	ATA Board of Directors Meeting 3:00 - 5:00 pm	Historical Vignette 3:45 - 4:30 pm	Oral Abstract (6) Sessions: 3:15 - 4:15 pm Clinical | Basic	Oral Abstract (4) Sessions: 3:15 - 4:15 pm Clinical | Basic	
5:00					
6:00	Women in Thyroidology 5:00 - 6:00	CME Symposium 4:30 - 5:45 pm	2 Simultaneous Symposia: 4:15 - 5:30 pm Clinical | Translational	2 Simultaneous Symposia: 4:15 - 5:30 pm Clinical | Translational	
7:00	Newcomers' Welcome 6:00 - 7:00	ATA Annual Business Meeting 5:45 - 6:45 pm (*ATA Members Only*)	CME Symposium 5:30 - 6:45 pm	ATA Banquet 7:30 - 11:00 pm *(Admission by ticket only)*	
	Welcome Reception 7:00 - 8:30	Free Evening	Academy of Clinical Thyroidologists (ACT) Meeting: 6:45 - 9:00 pm		

Meeting schedule may change. Check *www.thyroid.org* for Meeting updates.

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